UNIVERSITY OF ALBERTA

A NEW POLYENE CYCLIZATION PROCESS PROMOTED BY THE CROSS CONJUGATED β-KETO ESTER SYSTEM

by

DUONG DUC-PHI TRAN

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **A NEW POLYENE CYCLIZATION PROCESS PROMOTED BY THE CROSS CONJUGATED β-KETO ESTER SYSTEM** submitted by **DUONG DUC-PHI TRAN** in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY**.

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DEDICATED TO MY FAMILY

Abstract

Under Lewis acid catalysis, the cross conjugated β-keto ester system was found to be an excellent promoter for polyene cyclization. A variety of enone esters were successfully prepared and their cyclization examined. The results demonstrate that this system could be effectively applied to promote cationic cyclization, which occurred readily with high regio- and stereoselectivity. In all the cases examined, the cyclization process produced exclusively a single polycyclic product having *cis* ring fusion. In essence, this cyclization process allows for expeditious construction of a variety of highly functionalized polycyclic ring systems, such as hydrophenanthrene, hydrochrysene and thiophene-containing systems.

The first chapter of this thesis describes the use of the cross conjugated β-keto ester system as a convenient and highly effective promoter to facilitate the intramolecular Friedel-Crafts alkylation leading to highly functionalized hydrophenanthrene (e.g., compounds **30** and **38**) and hydrochrysene (e.g., compounds **46**, **47** and **49**) systems. For example, in the synthesis of compound **38**, enone ester **33** was readily prepared in five steps starting from the commercially available 3-ethoxy-2-cyclohexenone. (Scheme 24). Treatment of **33** with stannic chloride in dichloromethane resulted in its cyclization to give hydrophenanthrene **38** in a quantitative yield after 30 min at -78°C. A similar polyene cyclization process was found to be effective for the construction of hydrochrysene system. Using the newly developed polyene cyclization process as a key operation, a synthetic approach towards pygmaeocyn C (**51**), a naturally occurring diterpenoid isolated from the roots of

Pygmaeopremna herbacea, was conceived. Preliminary results are also discussed in this chapter.

The second chapter presents the successful application of the polyene cyclization process to facilitate the synthesis of polycyclic thiophene-containing compounds which may have desirable medicinal properties. A number of highly functionalized tricyclic thiophene-containing compounds were prepared (e.g., compounds **76**, **79**, **89** and **92**) *via* polyene cyclization promoted by the cross conjugated β-keto ester system. This key process proved to be extremely effective. As illustrated in Scheme 49, tricyclic compound **76** was produced quantitatively upon treatment of enone ester **72** with stannic chloride. In a similar manner, compounds **79**, **89** and **92** were readily synthesized in uniformly high yield.

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List of Abbreviations

a	anti-phase
Ac	Acetyl
Ac_2O	Acetic anhydride
Anal.	elemental analysis
APT	Attached Proton Test
br	broad
Bu	butyl
calcd.	calculated
d	doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
eq.	equivalent
Et	ethyl
Et_2O	diethyl ether
FTIR	Fourier Transform Infrared Spectroscopy
h	hour
HMPA	Hexamethylphosphoramide
hrms	High Resolution Mass Spectrometry
Hz	Hertz
J	coupling constant
ir	Infrared Spectroscopy

LDA	Lithium Diisopropylamide
m	multiplet
M	Molar
M^+	Molecular ion
Me	methyl
MHz	Megahertz
min	minute
mL	milliliter
mmol	millimole
mol	mole
mp	melting point
Ms	Mesyl
MVK	Methyl Vinyl Ketone
m/z	mass to charge ratio
NBS	*N*-Bromosuccinimide
nmr	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Enhancement
p	para
p	phase
PPC	Pyridinium Chlorochromate
p-TsOH	*p*-Toluenesulfonic Acid
Ph	Phenyl
py	pyridine
q	quartet
R	generalized alkyl group or substituent
rt	room temperature

s	singlet
SET	Single Electron Transfer
t	tertiary
t	triplet
TEA	triethylamine
THF	Tetrahydrofuran
tlc	thin-layer chromatography
Ts	toluenesulfonyl

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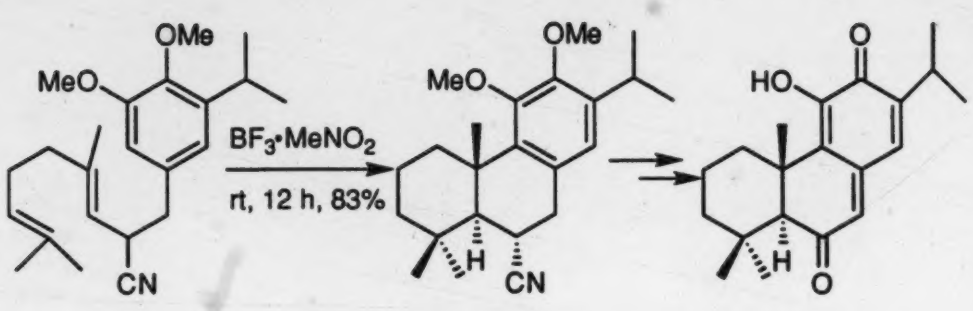
CHAPTER ONE

Application to the synthesis of hydrophenanthrenes and hydrochrysenes

INTRODUCTION

Intramolecular Friedel-Crafts alkylation *via* cationic intermediates has continued to engage the attention of the chemist over the years. In the context of polyene cyclization, intramolecular Friedel-Crafts alkylation continues to offer innovative contributions, with highlights that are regarded as methods of choice for the synthesis of cyclic molecules. The first typical Friedel-Crafts alkylation reaction was reported as the reaction of benzene with amyl chloride in the presence of aluminum chloride to produce amylbenzene which was carried out by Charles Friedel and his American collaborator James Mason Crafts in Paris on May 14, 1877. Since the recognition of the practical importance of this discovery, intramolecular alkylation aspect of Friedel-Crafts chemistry has gained increasing popularity and has been extensively investigated and successfully applied to the synthesis of complex natural products. For example, treatment of aromatic diene **1** with the $BF_3 \cdot MeNO_2$ complex yielded a single isomeric product **2**, a valuable intermediate for the synthesis of antineoplastic agent taxodione **3** (Scheme 1).[1]

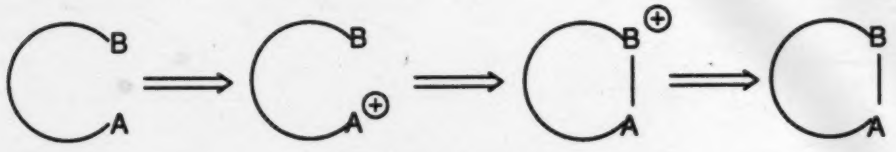
The fact that the molecules of nature mostly possess cyclic components (either as part of the molecule or as the molecular skeleton) has made the cyclization reaction one of the most important arts of organic synthesis. Continuous and all-round efforts in this area are manifested in the improvement of existing methodologies and in the discovery of new methods and new reagents. As mentioned above, in the context of the polyene cyclization chemistry, intramolecular Friedel-Crafts alkylation has been proven to be a very powerful



1 2 3

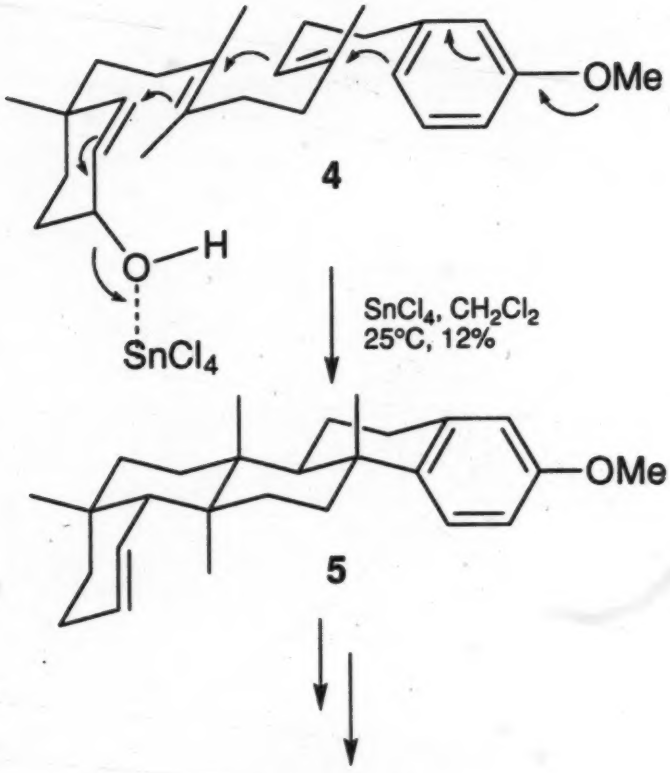
Scheme 1

synthetic tool for the preparation of polycyclic compounds. Its attractiveness lies in the potential control of stereochemistry and the readiness with which highly substituted carbon-carbon bonds may be formed. As depicted in Scheme 2, it can be seen that the reaction constitutes the formation of a bond between A and B, which effectively transforms an open chain structure into a cyclic form. Extending along this basis, later studies have worked on connecting several bonds at a time to build a polycyclic structure in one operation. Such polycyclization or tandem cyclization, as the reaction is more popularly called, may lead to linear polycyclic compounds. A selective example is demonstrated in Scheme 3 with the allylic alcohol-initiated polyolefin cyclization of compound



Scheme 2

4 leading to the formation of compound **5** which is a desired intermediate for the synthesis of alnusenone.[2] According to the Stork-Eschenmoser postulate,[3] the transformation of *trans* double-bond geometry into *trans* ring-fusion stereochemistry in this process can be stereoelectronically rationalized in such a way that the cyclization occurs *via* chair-like conformations of the nascent rings and that the addition to each double bond takes place in an antiparallel fashion.

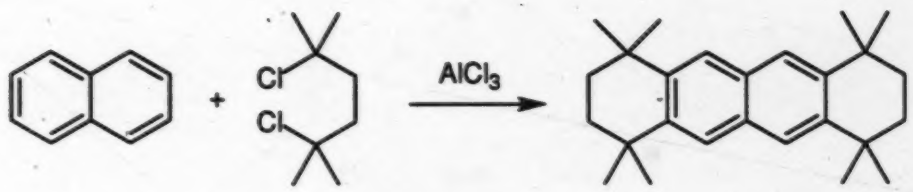


Alnusenone

Scheme 3

Although the Stork-Eschenmoser hypothesis, in general, allows good prediction of the relative stereochemistry of the cyclization products and establishes a synthetic strategy, the hypothesis is not universally applicable.[4]

In addition to the foregoing systematic applications of intramolecular Friedel-Crafts alkylation to the synthesis of indan and tetralin derivatives, intramolecular Friedel-Crafts alkylations have extensively been used to produce higher condensed ring systems, that is, systems with more than two condensed rings, which are referred as polycyclic compounds or polycyles. Polycycles prepared in this manner have long served as intermediates in the preparation of steroids,[5,6] alkaloids,[7,8] and terpenes.[9] In fact, there has been a flood of publications in the area of intramolecular Friedel-Crafts alkylation. However, with our intention, we would like to limit ourselves to the course of intramolecular Friedel-Crafts monocyclization leading to six-membered ring formation.

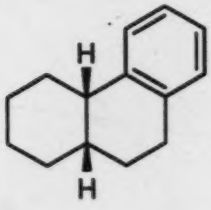


Scheme 4

In general, there are three main routes reported for the synthesis of polycyles by Intramolecular Friedel-Crafts alkylations. The first of these routes involves the intermolecular alkylations of the aromatics with difunctional alkylating agents.

This method was originally defined as Friedel-Crafts cyclialkylation by Bruson and Kroeger.[10] An example of this type is depicted in Scheme 4. The second route, which has been thoroughly studied by Ansell and co-workers,[11] entails multiple intramolecular ring closures of aryl-substituted unsaturated long-chain alcohols, acids, ethers and their derivatives in the presence of acid catalysts. A selective example is shown in Scheme 3 above.

The last, but most convenient, synthetic route for the preparation of polycyles involves the cyclization of aralkylcycloalkanols, aralkylcycloalkenes, aralkylcycloalkenones and related systems in the presence of acid catalysts. In fact, this method has been extensively investigated by numerous research groups toward the synthesis of hydrophenanthrene derivatives.[12] Fundamentally, ring closure to form six-membered ring on the system of alkanol derivatives may result in *cis* and/or *trans* fusion of rings A and B with varying amounts of spiranes as illustrated below with compounds **6**, **7** and **8** respectively. As described by Barnes and co-workers,[13] the formation of these isomeric products depends on various factors including reaction conditions, catalyst type, and both structural and electronic nature of the cyclized substrate. Based on their results, they have drawn a mechanism in which various possible



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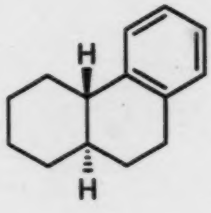

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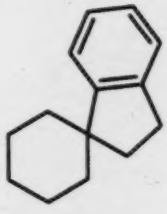
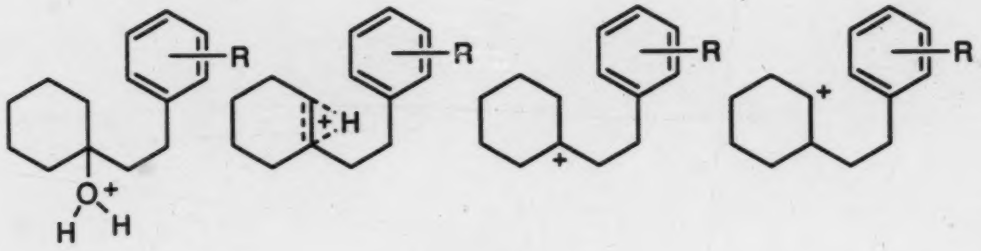


8

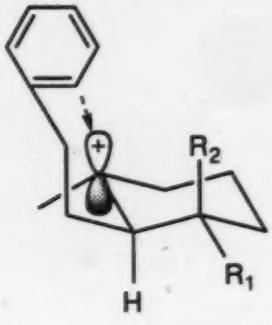
cationic intermediates are in competition with each other as represented in Scheme 5. They speculated that the cyclizations of alcohols with a moderately reactive group such as phenyl proceeded mainly *via* the bridged ion to yield *cis*-hydrophenanthrene,[13] whereas with a more reactive aryl group such as *m*-methoxyphenyl the cyclization proceeded largely through the tertiary carbocation to yield spirane,[14] and with unreactive aryl groups such as *o*-chlorophenyl the cyclization occurs *via* a secondary carbocation to produce *trans*-hydrophenanthrene.[13]



Scheme 5

More recently, the stereochemical mode of the reaction has alternatively been explained by considering the conformation of the intermediate carbocation. If the intermediate has a conformation depicted in structure **9** in which the parent cyclohexyl ring has the chair conformation and the bulky substituent prefers the equatorial position, then an easy overlap of the empty *p* orbital of the secondary carbocation of the cyclohexyl ring is obvious. This will therefore result in the observed *cis* fusion, that is in consistent with axial attack of the aromatic ring. On the other hand, if the intermediate **10** is invoked, in order to produce a *trans*

fusion, it is obvious that overlap of the *p* orbital and cabocation center is hardly facilitated, so *trans* fusion is not observed. However, the stereochemical outcome of intramolecular Friedel-Crafts alkylation depends on the bulkiness of existing functional groups and the substitution pattern on the aromatic ring, and thus reflects the propensity for different conformations of a compound in the transition state.[15]



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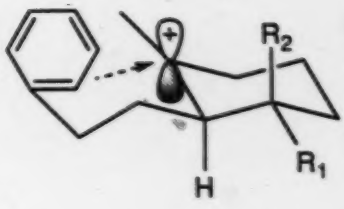
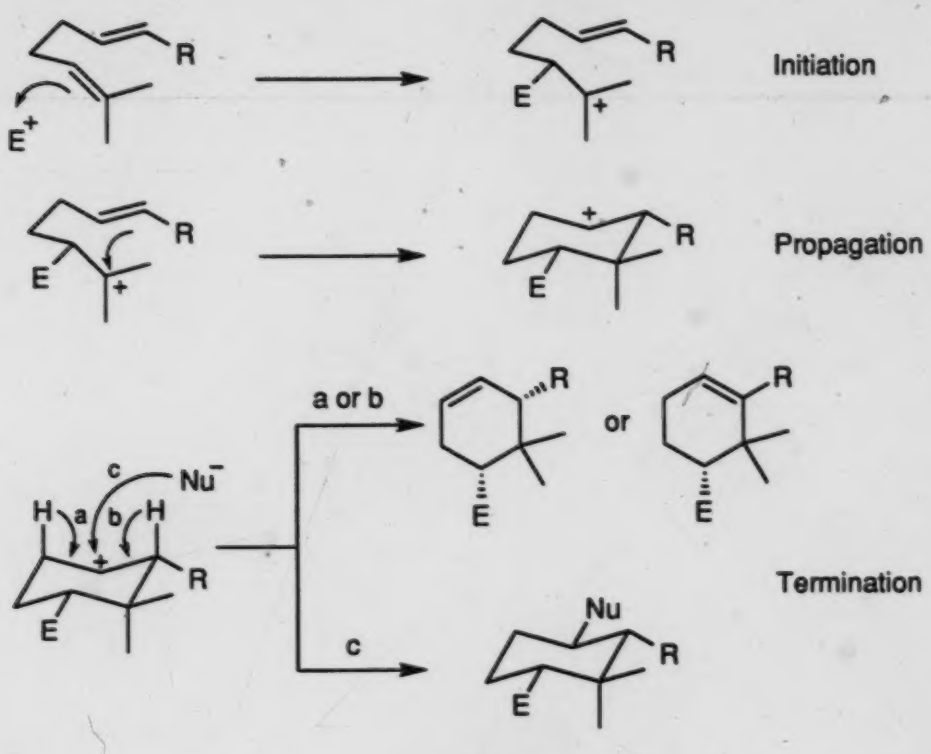


10

It is worth noting that six-membered ring formation is, by far, the most common mode of monocyclization, and it can be achieved using a variety of electrophilic reagents. In general, the success of the polyene cyclization process depends on the method of initiation, the nucleophilicity of the double bonds involved, and the mechanism of termination.[16] Although there is unlikely to be a unique mechanism for all polyene cyclization processes, a simplified representation involving carbocations is depicted in Scheme 6 with a simple 1,5-diene as an example. However, this does not exclude concerted and partly concerted mechanisms.

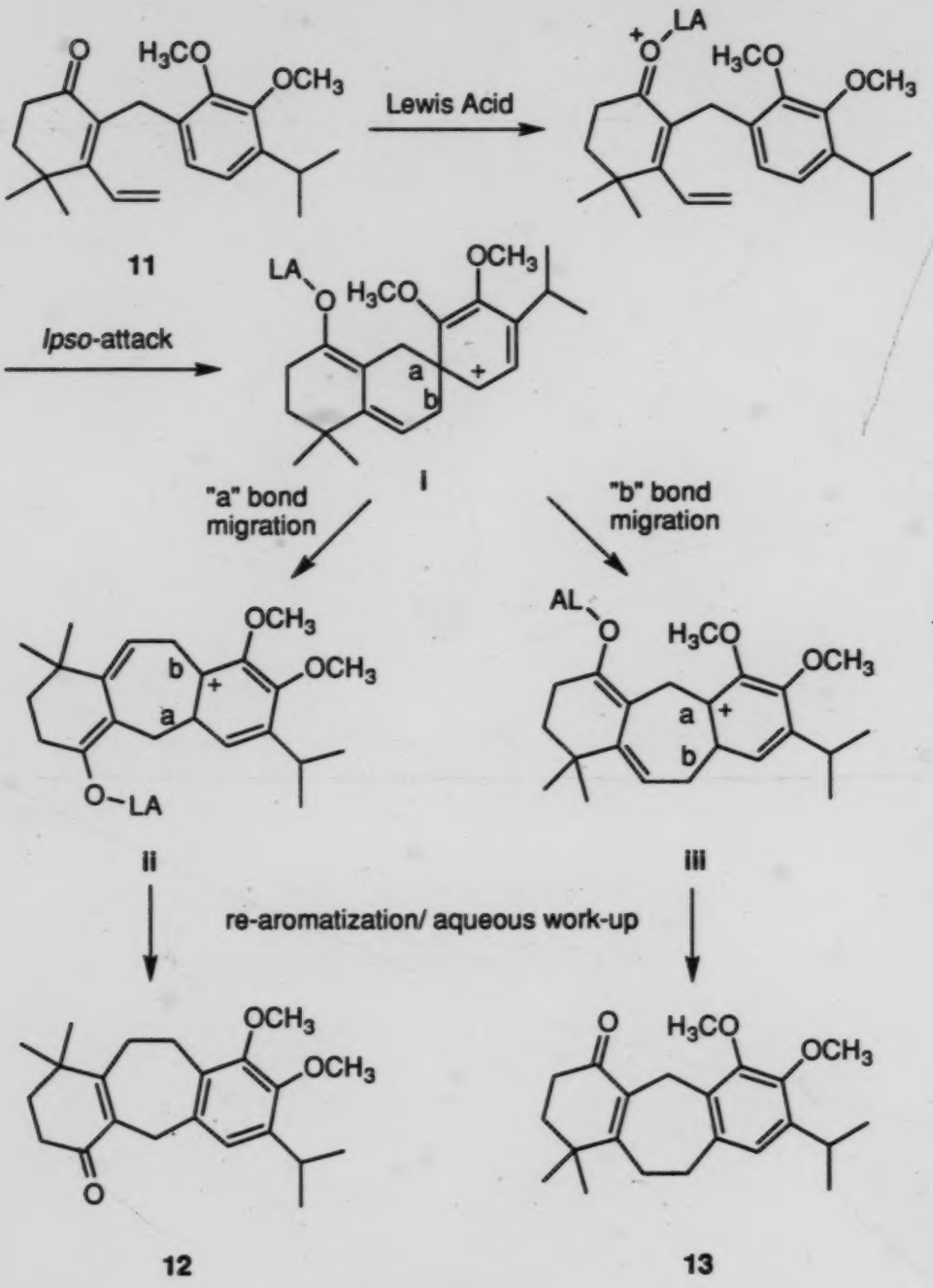


Scheme 6

From a synthetic point of view, the ideal polyene cyclization would terminate by one mechanism giving a single product. Unfortunately, terminaiton, as seen in Scheme 6 above, can be achieved by either elimination of a proton or attack by an internal or external nucleophile. Proton elimination can, in principle, be regioselective or random. This complication of many possibilities of termination can provide unpredictable outcomes when alkenes terminate cyclization. As a result, extensive studies on the process of termination have been carried out by different research groups[17] and have thus led to the development of terminators whereby the products can be precisely anticipated.[16] One of the favorable

answers to the question of how to remove any ambiguity concerning the structure of the product is the use of an aryl or heteroaryl ring as the terminating group, particularly if they are electron rich. However, when they (the aromatic rings) are appropriately substituted, they too can give mixtures of positional isomers. For example, Majetich and co-workers have examined in detail the rearrangement of compound **11**, when treated with Lewis acids[18] as Scheme 7. According to their fundamental mechanistic studies, an *ipso*-attack mechanism accounts for the production of enones **12** and **13**. *ipso*-Attack by the arene on the electrophilic dienone unit leads to the formation of cation **I**, which can generate intermediates **II** or **III** by migration of the "a" or "b" bond, respectively.

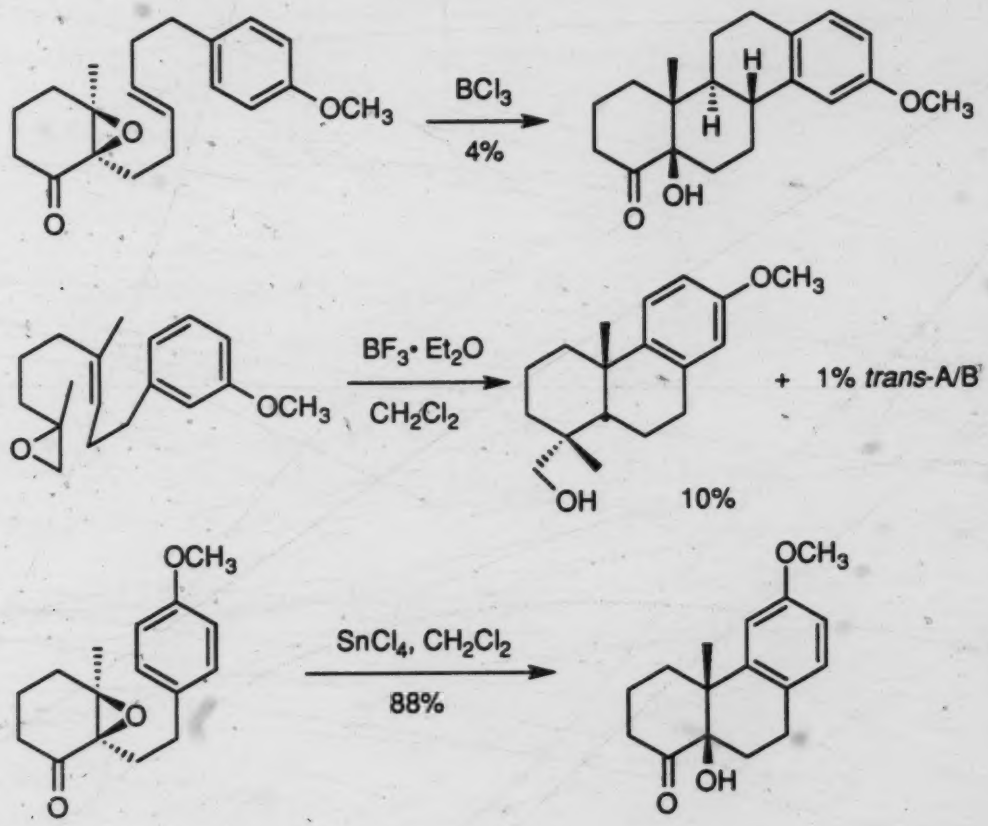
An equally important factor that can affect the success of polyene cyclization is the choice of initiators. In general, the cyclization can be initiated by formation of a cation either by electrophilic addition to a double bond or by ionization, usually from an sp^3 hybridized carbon. Bronsted and Lewis acids have been the most frequently used electrophiles. Protonation of the terminal olefinic bond was used in early attempts to initiate polyene cyclization. Unfortunately, these reactions resulted in complex mixtures of partially cyclized products.[19] The difficulties encountered were attributed to the lack of regioselectivity in the protonation process as well as the occurrence of competing reactions, such as addition and isomerization, due to the strong conditions generally applied. Therefore, the use of an appropriately positioned functional group as an initiator is a common practice.


Lewis Acid
11
Ipso-attack
I
"a" bond migration
"b" bond migration
ii
iii
re-aromatization/ aqueous work-up
12
13

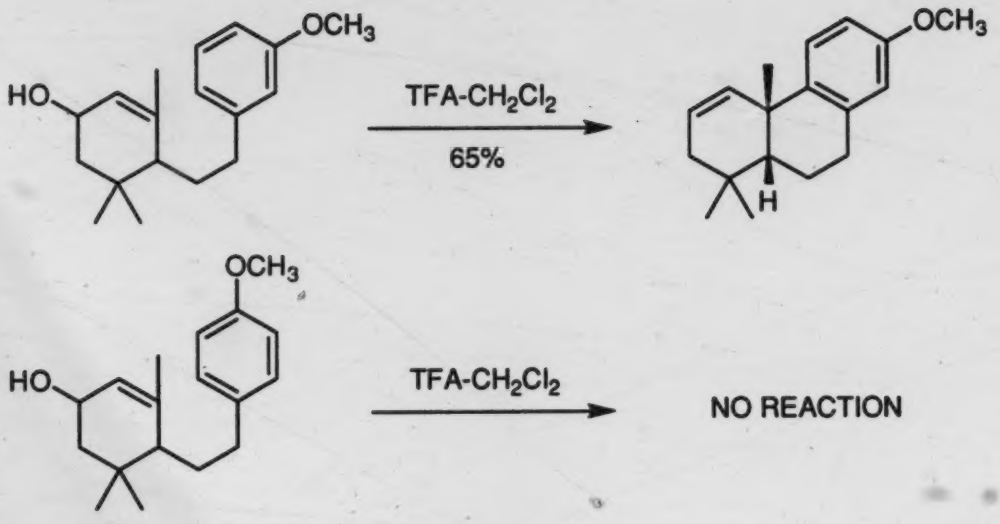
Scheme 7

The use of epoxide as the initiating functionality in a polyene cyclization process which is terminated by aromatic rings has been investigated by different research groups.[20] However, from the preparative viewpoint, it is only useful for monocyclizations, whereas bi- and tri-cyclizations occur in poor yields. This comparision is clearly illustrated in Scheme 8 below.

Initiation by the use of allylic alcohol functionality in the intramolecular Friedel-Crafts monocyclization has been studied by Davis in 1978.[21] In this report, the

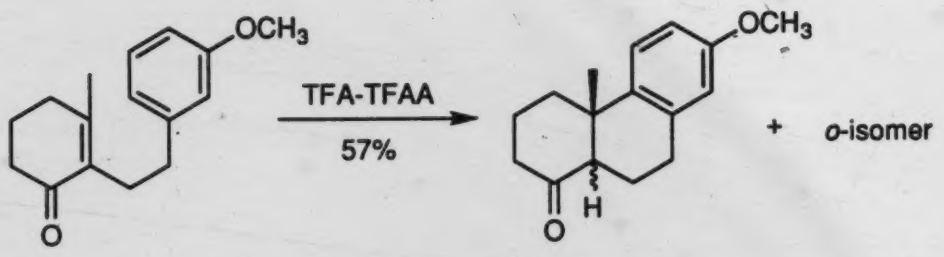


Scheme 8



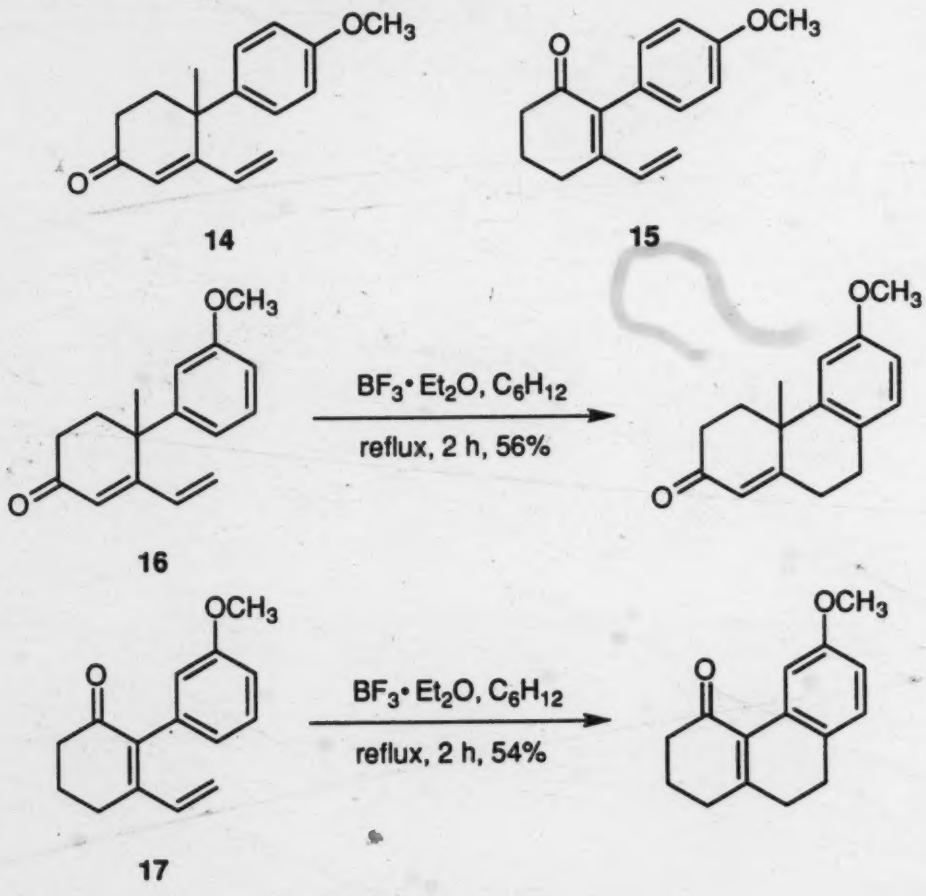
Scheme 9

cyclization leading to podocarpatrienes was shown to be facile when the methoxy substituent on the aromatic ring is *para* to the reaction site. However, when the methoxy group is *meta* to the site of electrophilic attack, the substrate underwent elimination upon acid treatment and yielded no tricyclic product (Scheme 9).



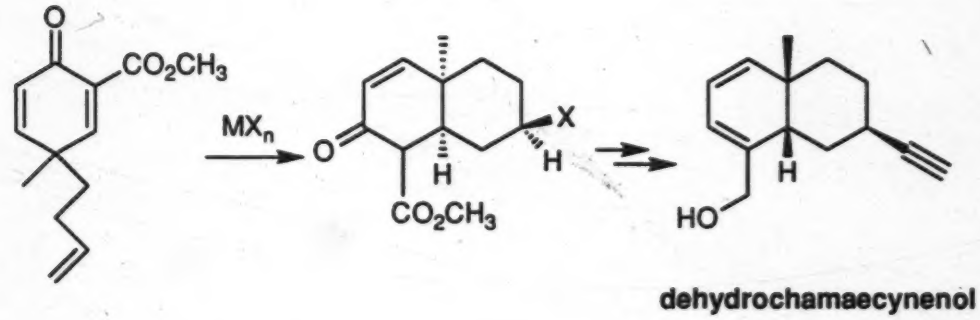
Scheme 10

In cyclization reactions, enones have been used by different groups[22] as precursors of oxyallyl cations by either protonation or by coordination with Lewis acids. It is notable that cyclization of enones, in many cases, does not provide high yields, and the reason for this may be attributed to the presence of the methyl group at the site of cyclization. An example is shown in Scheme 10, in which the anisyl ring is an efficient terminator and reacts mainly *para* to the methoxy, but *ortho* reaction is also found.



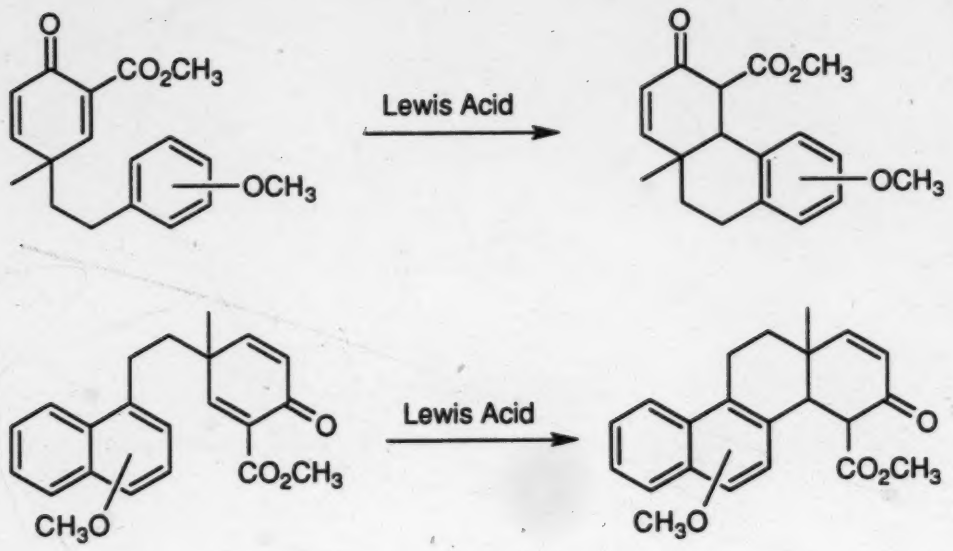
Scheme 11

Recently, Majetich[23] reported a new method for the preparation of hydrophenanthrenes employing fully conjugated dienone as an initiator. With varying degree of success, he has shown that compounds **14** and **15**, with the methoxy group substituted at the *meta* position relative to the site of cyclization (Scheme 11), are precluded from cyclization. This can be attributed to the directing nature of the methoxy group. In contrast to these examples, treatment of aryl-dienones **16** and **17** with boron trifluoride etherate in refluxing cyclohexane produces cyclization products in comparable yields (Scheme 11).



Scheme 12

In the development of new initiators, we have recently developed a new method for polyene cyclization that is promoted by the cross conjugated β-keto ester system. This system has been an excellent initiator that can effect efficient construction of polycyclic carbocyclic systems[24] (Scheme 12), and the efficiency of this method has been demonstrated in the total synthesis of the acetylenic sesquiterpene dehydrochamaecynenol.[25] In principle, by replacing the terminal double bond of the side chain with an aromatic ring system, we can



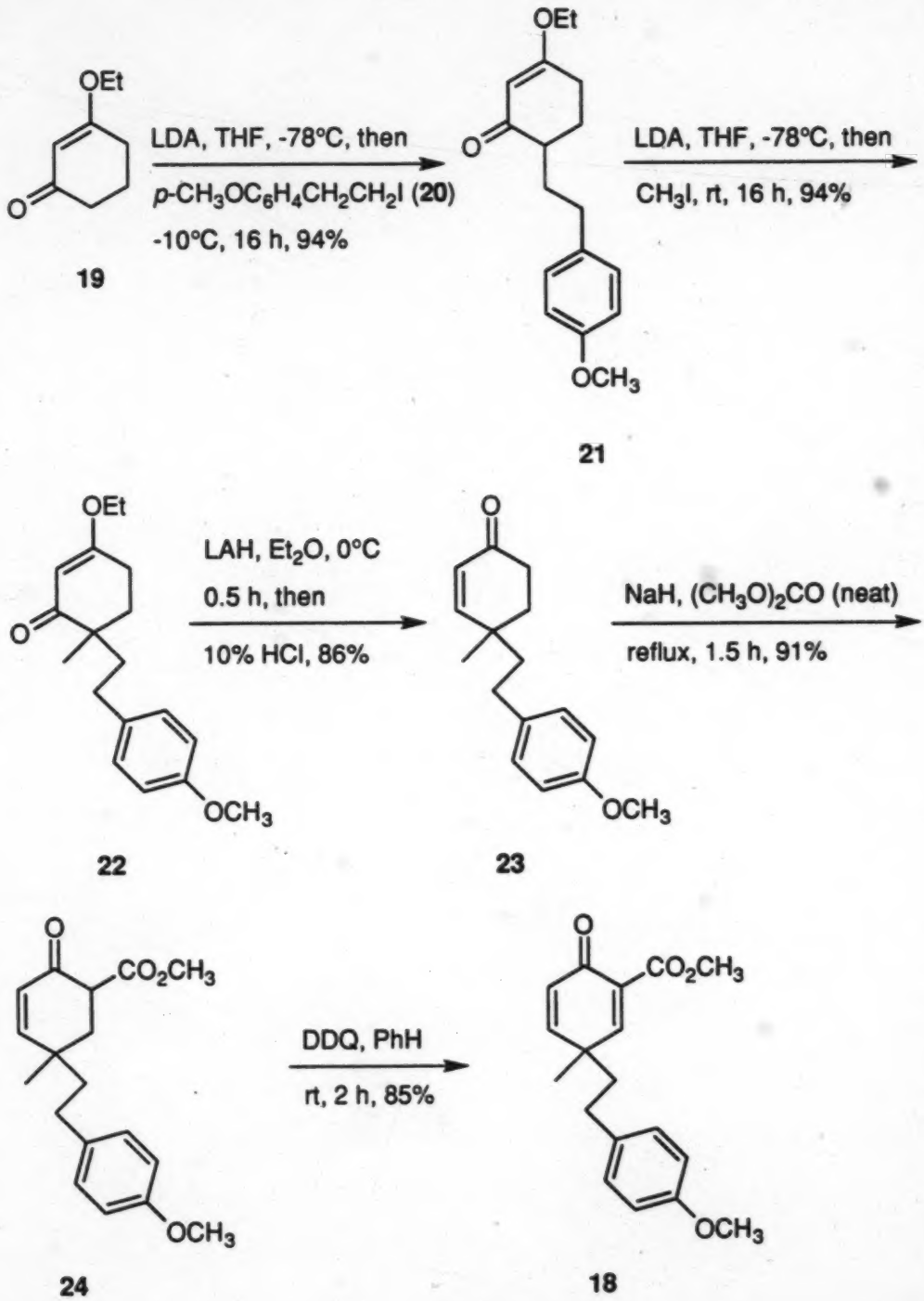
Scheme 13

readily construct an aromatic fused polycyclic carbon skeleton. If so, this annulation would represent a new method for the preparation of highly functionalized hydrophenanthrenes and hydrochrysenes (Scheme 13). As a result, we have carried out an extensive study on the intramolecular Friedel-Crafts alkylation promoted by the cross conjugated β-keto ester system and the results will be discussed in this chapter of the thesis. In addition, the results from our newly developed polyene cyclization process have prompted us to undertake the synthetic studies towards the total synthesis of pygmaeocin C, a naturally occurring diterpenoid isolated in 1990 from the roots of *Pygmaeopremna herbacea* . This will also be discussed in this chapter.

RESULTS AND DISCUSSION

Our initial investigation on polyene cyclization promoted by the cross conjugated β-keto ester system was carried out on the dienone ester **18**. This compound was readily prepared from the commercially available 3-ethoxy-2-cyclohexenone **19** *via* a sequence involving five synthetic operations as shown in Scheme 14.

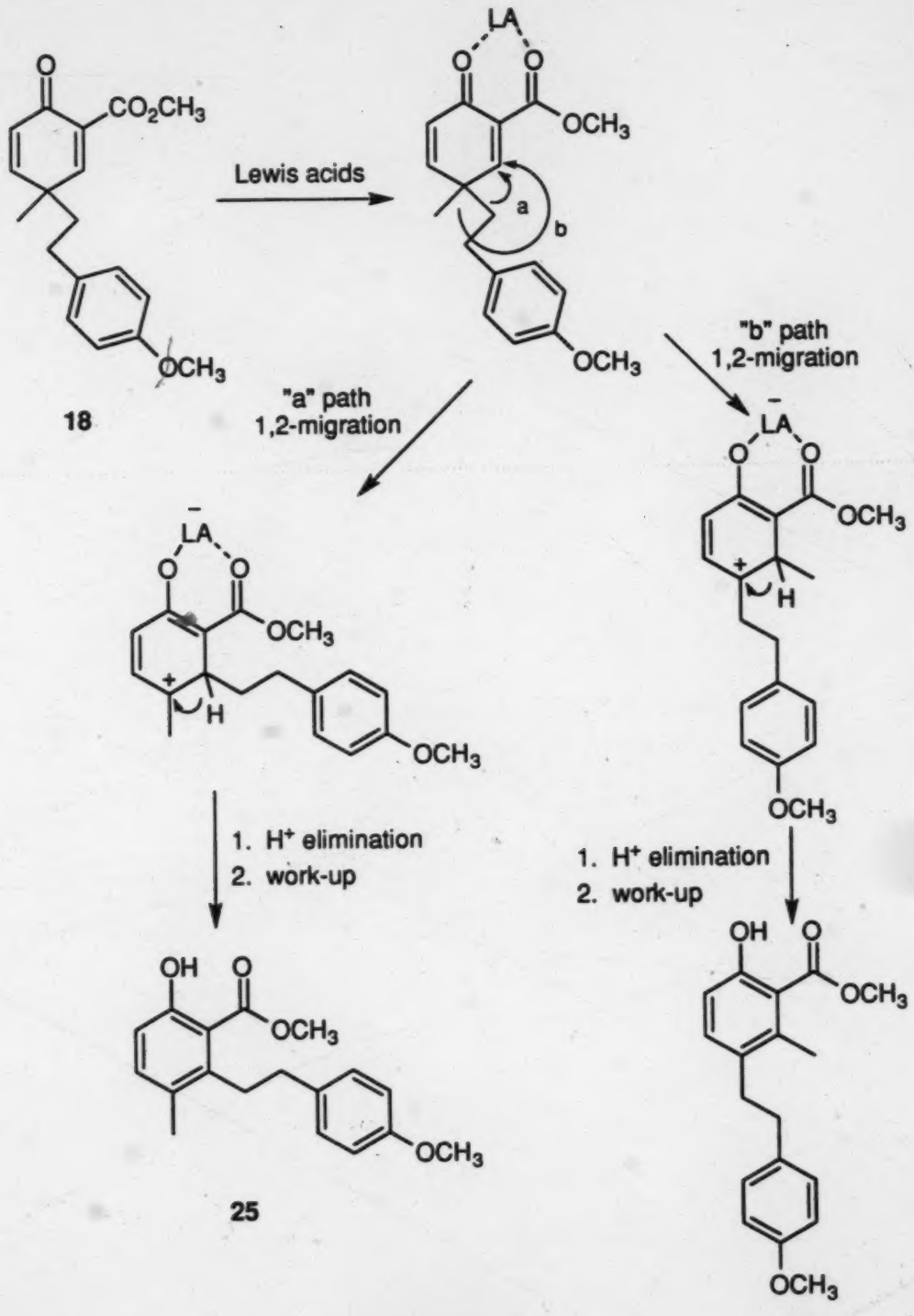
Stork-Danheiser alkylation of enone **19** with lithium diisopropylamide (LDA) and 2-(4-methoxyphenyl)ethyl iodide **20** which was prepared in sufficiently high yield from its corresponding alcohol, followed by flash chromatography gave compound **21** in 94% yield. This compound was then methylated using lithium diisopropylamide as the base providing the dialkylated product **22** in 94% yield. The structure of **22** was assigned by spectroscopic methods. The infrared (ir) spectrum showed a carbonyl absorption at 1651 cm^{-1}, indicating the presence of an enone. In the proton nuclear magnetic resonance (^1H nmr) spectrum, two doublets at δ 7.08 and 6.80 with the same coupling constant (J = 9 Hz) were attributed to the four protons on the aromatic ring. The vinylic proton of the enone moiety appeared at δ 5.27 as a singlet. The methyl group appeared at δ 1.14 also as a sharp singlet. The high resolution mass spectrum showed a molecular ion peak at m/z 288.1725, corresponding to the molecular formula $C_{18}H_{24}O_3$. The elemental analysis was also in agreement with the molecular composition. Compound **22** was then reduced with lithium aluminum hydride, followed by hydrolysis with 10% hydrochloric acid to give **23** in 86% yield over two steps. In the ^1H nmr spectrum, it displayed two doublets at δ 6.72 and 5.91 with the same coupling constant (J = 10 Hz) belonging to the two vinylic protons


OEt
O
LDA, THF, -78°C, then
p-CH3OC6H4CH2CH2I (20)
-10°C, 16 h, 94%
19
OEt
O
OCH3
21
LDA, THF, -78°C, then
CH3I, rt, 16 h, 94%
OEt
O
LAH, Et2O, 0°C
0.5 h, then
10% HCl, 86%
OCH3
22
O
OCH3
23
NaH, (CH3O)2CO (neat)
reflux, 1.5 h, 91%
O
CO2CH3
OCH3
24
DDQ, PhH
rt, 2 h, 85%
O
CO2CH3
OCH3
18

Scheme 14

of the enone moiety. The ir spectrum confirmed the presence of an enone with a strong absorption at 1681 cm^{-1}. In the high resolution mass spectrum, a molecular ion peak at m/z 244.1455 was consistent with the molecular formula $C_{16}H_{20}O_2$.

Compound **23** was treated with sodium hydride in refluxing dimethyl carbonate. The desired product **24** thus formed exclusively in 91% yield was shown to exist as a mixture of two epimers and an enol tautomer in a ratio of 5:3:2 respectively as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{18}H_{22}O_4$ by its high resolution mass spectrum displaying a molecular ion peak at m/z 302.1520. The second conjugated double bond of **18** was constructed using a 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation method. Thus, compound **24** was treated with DDQ in anhydrous benzene at room temperature for about two hours to give 85% yield of the required dienone ester **18** for cyclization. In the ir spectrum, two carbonyl absorption bands were displayed at 1743 (ester) and 1665 cm^{-1} (ketone). In the ^1H nmr spectrum, the three olefinic protons were shown at δ 7.51 (d, J = 3 Hz, H_3), 6.78 (dd, J = 3 and 10 Hz, H_5) and 6.35 (d, J = 10 Hz, H_6). The presence of the aromatic ring was indicated by the two doublets at δ 7.00 and 6.80 with the same coupling constant (J = 9 Hz). The signals of two OCH_3 were each shown as a singlet at δ 3.85 and 3.77, and an additional methyl singlet was observed at δ 1.35. In the high resolution mass spectrum, dienone ester **18** showed a molecular ion peak at m/z 300.1362 in agreement with the molecular formula $C_{18}H_{20}O_4$.

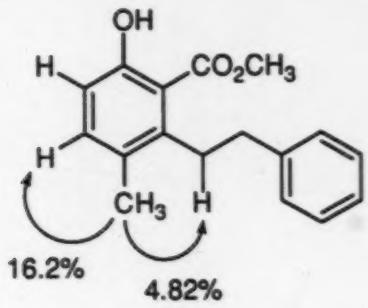

LA
O
O
CO_2CH_3
OCH_3
Lewis acids
a
b
OCH_3
18
"a" path
1,2-migration
"b" path
1,2-migration
LA
O
O
OCH_3
H
OCH_3
1. H^+ elimination
2. work-up
OH
O
OCH_3
OCH_3
25
1. H^+ elimination
2. work-up
OH
O
OCH_3
OCH_3
26

Scheme 15

With dienone ester **18** in hand, we were able to study its mode of cyclization using various Lewis acids. Our initial attempt was to carry out the cyclization reaction using stannic chloride ($SnCl_4$) as the Lewis acid. Unfortunately, treatment of compound **18** with stannic chloride in dichloromethane at room temperature for 16 hours gave only the rearrangement products **25** and **26** in 19:1 ratio in a combined yield of 56%. This rearrangement process occurred presumably *via* 1,2-migration of one of the side chains followed by proton elimination as shown in Scheme 15. This process is often called the *dienone-phenol rearrangement*.[26] As most of their signals was overlapped, only the structure of the major product (**25**) was assigned by spectroscopic methods and NOE experiments. In the ^1H nmr spectrum, a sharp singlet at δ 10.63 was easily recognized for the phenolic proton. The two aromatic protons of the phenolic ring appeared at δ 7.24 and 6.81, both as a doublet with the same coupling constant (J = 8.5 Hz). From this coupling pattern, it is obvious that these two aromatic protons have an *ortho* relationship. The existence of the aromatic ring of the intact side chain was evidenced by the two doublets with the same coupling constant (J = 9 Hz) at δ 7.14 and 6.87. The regiochemistry of the products was further confirmed by NOE experiments on the major isomer. As shown in Figure 1, irradiation of the C_4 methyl at δ 2.30 resulted in enhancement of H_5 (16.2%) and the methylene protons adjacent to the phenolic ring (4.8%). However, in addition to overlapped signals, two singlets at δ 3.98 and 2.28 were indicative of the existence of **26**. Similar results were obtained when stannic chloride was replaced by aluminum chloride.

The above results clearly indicated that the migration of the side chains occurred at a faster rate than the desired polyene cyclization because of the

stability of the carbonium ion produced from the migration process. One possible solution to this problem would be to remove the carbon-carbon double bond of the parent cyclohexyl ring in compound **23** in order to reduce the stability of the carbonium ion, and thus suppress the side chain migration.

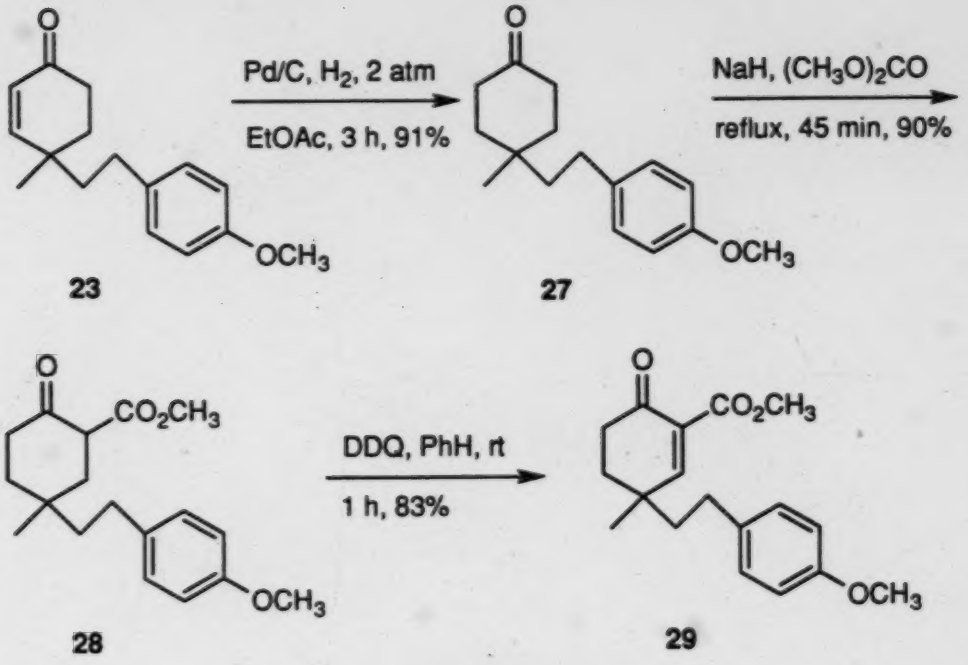


25

Figure 1

Towards this end, enone **23** was subjected to catalytic hydrogenation with 5% Pd/C using ethyl acetate as the solvent to give ketone **27** in 91% yield (Scheme 16). Carbomethoxylation of **27** with dimethyl carbonate and sodium hydride afforded 90% yield of compound **28** after 45 minutes, which existed mostly in the enol form as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{18}H_{24}O_4$ by the high resolution mass spectrum displaying a molecular peak at m/z 304.1668. Oxidation of **28** with DDQ in benzene at room temperature gave the required enone ester **29** in 83% yield. The ir spectrum of compound **29** showed two carbonyl absorptions at 1743 and 1686 cm^{-1}, indicating the presence of an ester and an enone, respectively. The structure of this compound was further corroborated by the signals in the ^1H nmr spectrum at δ 7.09 (d, J = 9 Hz, 2 x ArH), 6.83 (d, J = 9 Hz, 2 x ArH), 3.81 (3H, s, OCH_3)

and 3.79 (3H, s, OCH_3). The vinylic proton appeared at δ 7.40 as a singlet and the methyl singlet was observed at δ 1.28. In the high resolution mass spectrum, enone ester **29** showed the molecular ion peak at m/z 302.1514 which was consistent with the molecular formula $C_{18}H_{22}O_4$.

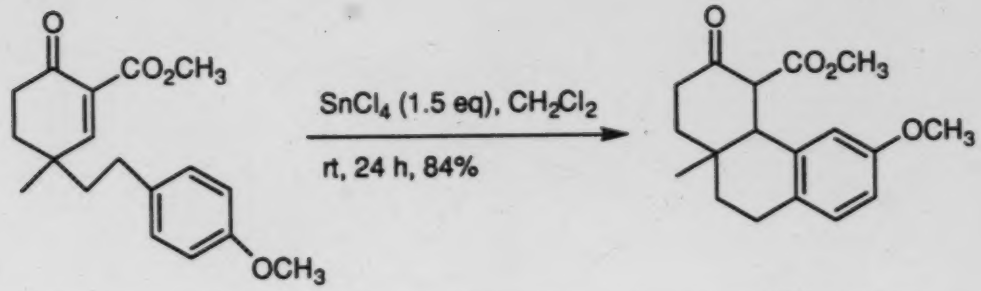


23 **27** **28** **29**

Scheme 16

When the enone ester **29** was subjected to treatment with stannic chloride, the desired cyclization was realized. After one day at room temperature, the desired hydrophenanthrene **30** was produced as the sole product in 84% yield (Scheme 17). Compound **30** showed a molecular ion peak at m/z 302.1516 in its high resolution mass spectrum, corresponding to the molecular formula $C_{18}H_{22}O_4$. This compound was obtained mostly in its enol form as indicated by ^1H nmr spectrum in which the signal of the hydroxyl group of the enol tautomer

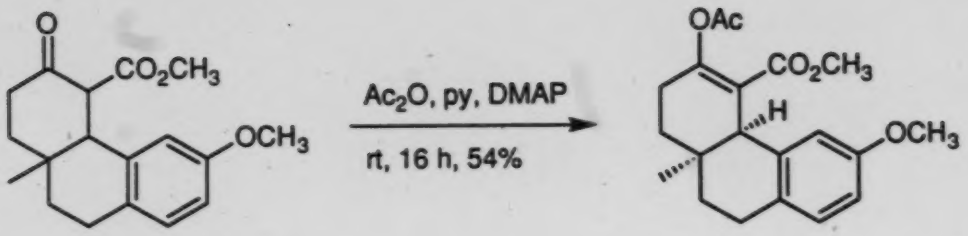
was shown at δ 12.60 as a sharp singlet. The regiochemistry and stereochemistry of this compound was established as follows. Treatment of compound **30** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **31** (Scheme 18) whose structure was confirmed by spectroscopic methods, especially nmr spectroscopy with the assistance of NOE experiments.



29 **30**

Scheme 17

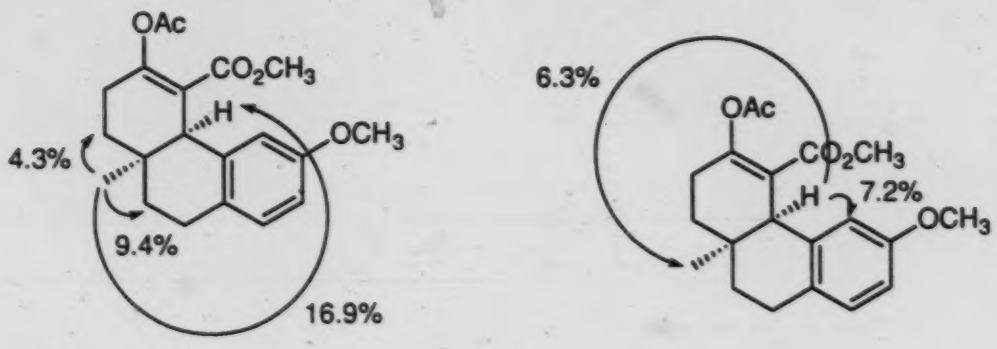
In its ir, spectrum, two carbonyl bands were displayed at 1763 cm^{-1} for enol acetate and 1718 cm^{-1} for ester functional groups accordingly, whereas an olefinic double bond absorption appeared at 1610 cm^{-1}. The high resolution mass spectrum showed a molecular ion peak at m/z 344.1620, corresponding to the desired molecular formula $C_{20}H_{24}O_5$, which was also supported by the elemental analysis. In the ^1H nmr spectrum, the singlet observed at δ 3.62 was attributed to the proton at the ring junction which was sufficiently shifted downfield due to the simultaneous deshielding effect of the aromatic ring and the double bond. The splitting patterns of the protons on the aromatic ring were noticed as a doublet with J = 9 Hz for the proton signal at δ 6.99, a doublet of



30 **31**

Scheme 18

doublets (J = 2.5 and 9 Hz) at δ 6.68, and another doublet (J = 2.5 Hz) for that at δ 6.65. These findings suggested that the aromatic protons had the required relationships (i.e. *ortho* and *meta*) in the assigned structure of compound **31**. In the ^{13}C APT nmr spectrum, a total of twenty signals was obtained in which the



31 **31**

Figure 2

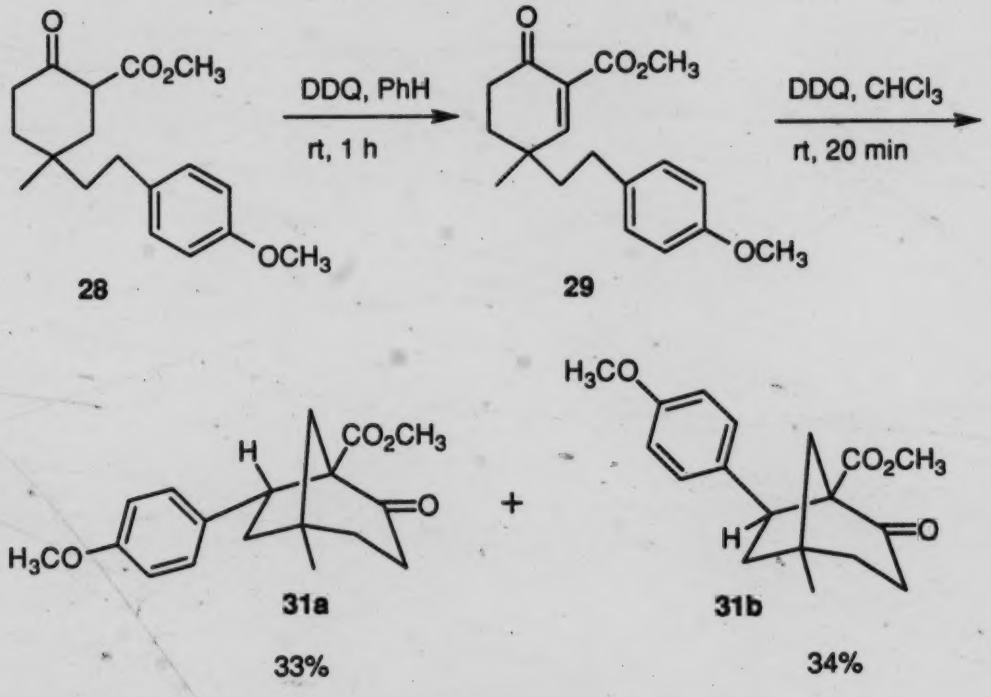
two carbonyl signals appeared at δ 157.9 and 155.4. All in all, the regiochemistry of the compound **31** was confirmed by its complete set of spectroscopic data, of which the ^1H nmr data are illustrated in Table 1, whereas

its ring junction stereochemistry was established by NOE experiments. As shown in Figure 2, irradiation of the ring junction methyl at δ 1.24 resulted in enhancements of proton at the ring junction (16.9%), a methylene proton at δ 1.79 (9.4%) and methylene protons at δ 2.28 (4.3%), whereas irradiation of the ring junction proton provided enhancements of the angular methyl (6.3%) and the adjacent aromatic proton (7.2%).

Table 1. ^{1}H nmr data of compound **31**

Proton	**δ** (in ppm)	**Multiplicity** (J in Hz)
Ar**H**	6.99	d (8.8)
Ar**H**	6.68	dd (2.5, 8.8)
Ar**H**	6.58	d (2.5)
OCH_3	3.73	s
OCH_3	3.70	s
ring junction **H**	3.62	s
2 x $ArCH_2$	2.69	dd (6.8, 6.8)
2 x CH_2	2.28	m
CH_3COO	2.20	s
CH_2	1.79	m
2 x CH_2	1.57-1.42	m
CH_2	1.35	m
CH_3	1.24	s

As a result of the above observations, it is clear that the α,β-unsaturated keto ester moiety in compound **29** can serve as an excellent promoter for cationic cyclization. The cyclization is highly efficient in terms of the yield of the product and the high degree of regio- and stereochemical control.



Scheme 19

On top of the above findings, there was a strange, yet interesting phenomenon observed with compound **29** when it was exposed to chloroform in the presence of DDQ. As shown in Scheme 19, treatment of the keto ester **28** with DDQ in dry benzene at room temperature for one hour provided presumably compound **29**, which upon exposure to chloroform in the presence of DDQ led to the unexpected formation of compound **31a** and its diastereomer **31b** in

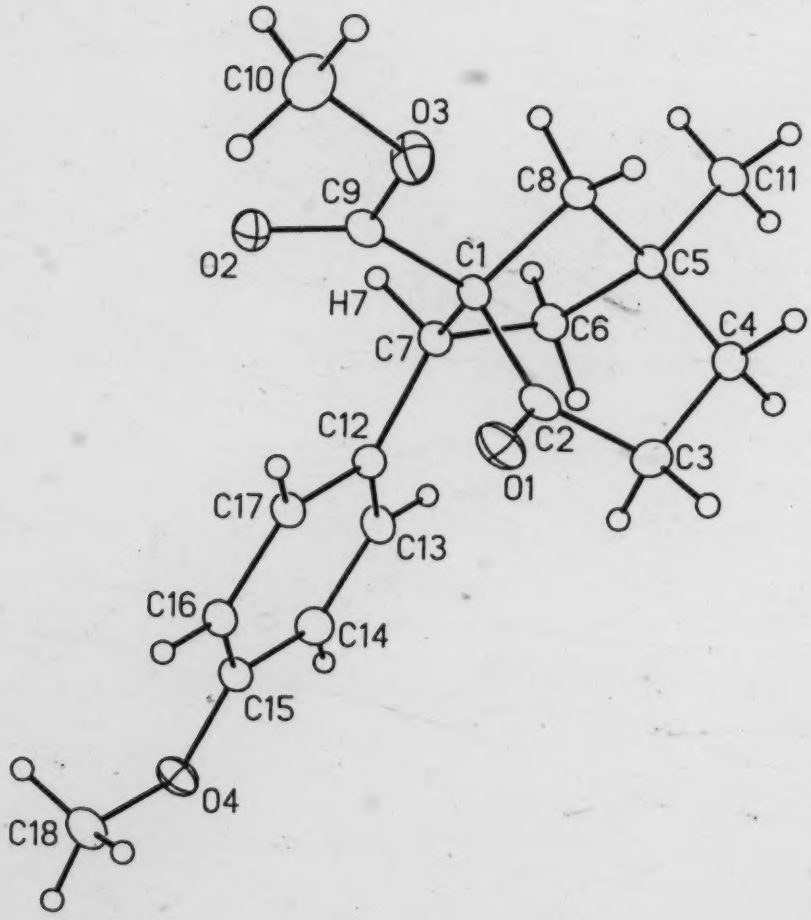


Figure 3. The three dimensional X-ray crystallographical structure of **31a**

virtually equal amount in a combined yield of 67% from **28**. Single crystal X-ray diffraction analysis unambiguously demonstrated the bond connectivity and relative stereochemistry shown in **31a** (Figure 3). At the first glance, we thought that the apparent trace amount of hydrochloric acid in chloroform has by itself induced the rearrangement process. It turned out to be not the case. When unsaturated keto ester **29** was stirred in chloroform for one day, the starting material was completely recovered. As a consequence, we believe that DDQ with the assistance of hydrochloric acid played an important role in the transformation of compound **29** to compound **31a** and **31b**.

$$RH_2 + DDQ \longrightarrow RH^+ + DDQH^- \longrightarrow R + DDQH_2$$

Scheme 20

It was reported[27] in the literature that the mechanism for the DDQ dehydrogenation basically takes place in two consecutive steps (Scheme 20). The initial step of the over-all reaction sequence is the hydride ion abstraction which is followed by proton elimination. However, catalysis by proton donors was explained as occurring through formation of the conjugate acid of the quinone, which species would be expected to be a far more powerful hydride ion abstractor than the neutral quinone (Scheme 21). Therefore, it seems reasonable that the formation of compound **31a** and **31b** results from the rearrangement process outlined in Scheme 22. Initially, the proton catalysis of DDQ provided the conjugate acid of quinone which then served as a powerful hydride ion abstractor and thus abstracted the benzylic hydride from compound **29**. This reversible process led to the formation of the cationic intermediate in

$$DDQ + HX \longrightarrow DDQH^+ + X^-$$

$$DDQH^+ + RH_2 \longrightarrow DDQH_2 + RH^+$$

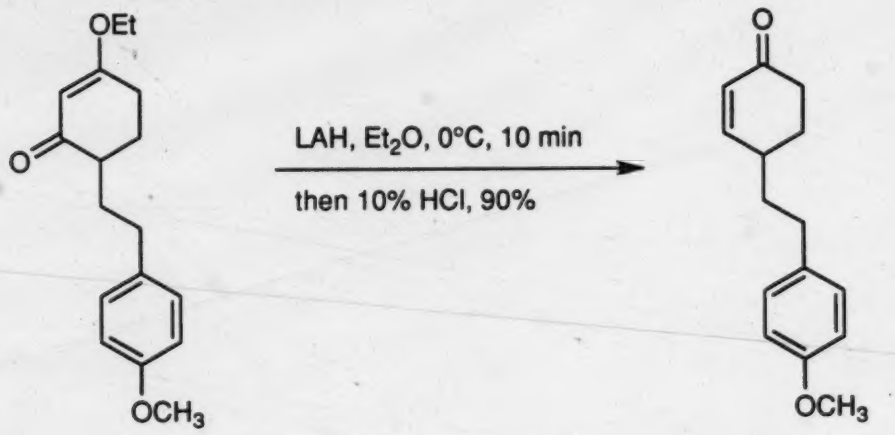
$$RH^+ + X^- \longrightarrow R + HX$$

Scheme 21

which the cationic center was stabilized by the anisyl group. This carbonium center was then overlapped by the π electron system of the nearby double bond giving rise to the production of the unstable cation **29a**. The subsequent hydride transfer reaction was followed to produce the observed products, **31a** and **31b**. The series of steps shown in Scheme 22, although credible in retrospect, were totally unexpected.

An additional work has been accomplished in this series of compounds in which compound **21** was utilized in the synthesis of 4-(*p*-methoxyphenylethyl)-2-cyclohexenone **32**, a naturally occurring ketone, that was first isolated from the gametophytic tissues of the foliose liverwort *Plagiochila longispina* from the Ecuadorian Andes.[28] Although many compounds produced by bryophytes have been shown to possess a wide variety of biological activities including allergenic, cardiotonic, carcinogenic, anti-inflammatory effects,[29] the biological activity of compound **32** remains to be studied. However, the motive for its synthesis is the use of the compound we have in hand to provide a more

efficient route than the existing ones.[28,30] As a result, starting from commercially available 3-ethoxy-2-cyclohexenone, ketone **32** was prepared *via* a simple two-step approach in 63% overall yield (Scheme 23).

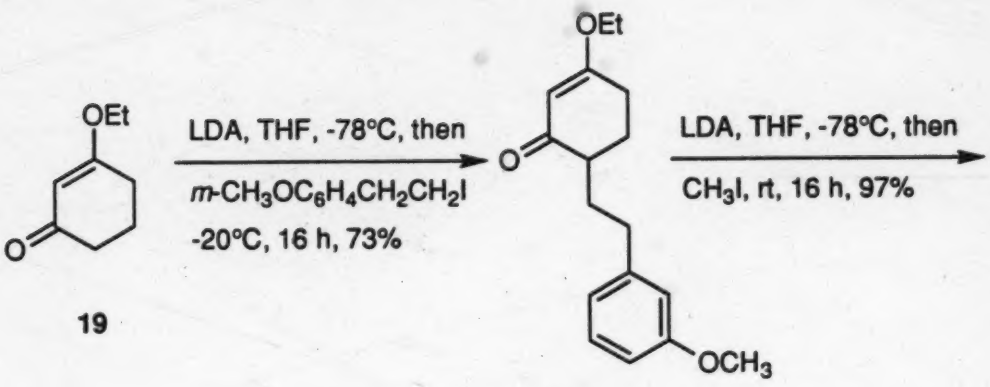


21 **32**

Scheme 23

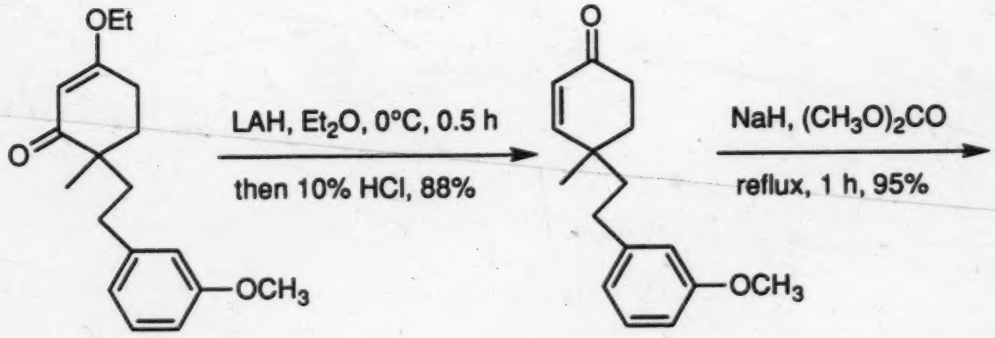
The encouraging results from the above studies led us to examine the influence of the C_4 side chain on the cyclization. Next, we decided to examine the cyclization mode of the compound containing an aromatic ring on the side chain with a methoxy group substituted at the *ortho*/*para* position relative to the site of cyclization. Thus, the required cross conjugated keto ester **33** was prepared from enone ether **19** according to Scheme 24.

Alkylation of **19** with LDA and 2-(3-methoxyphenyl)ethyl iodide, which was again prepared from its corresponding alcohol, in 86% yield afforded compound **34**. This compound was then methylated using LDA as the base in



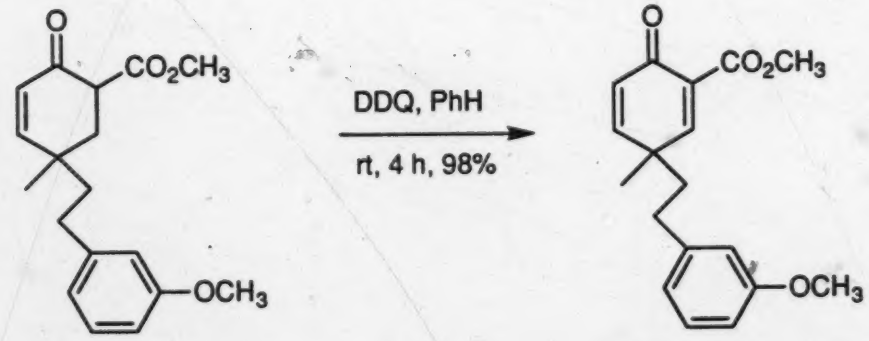
19

34



35

36



37

33

Scheme 24

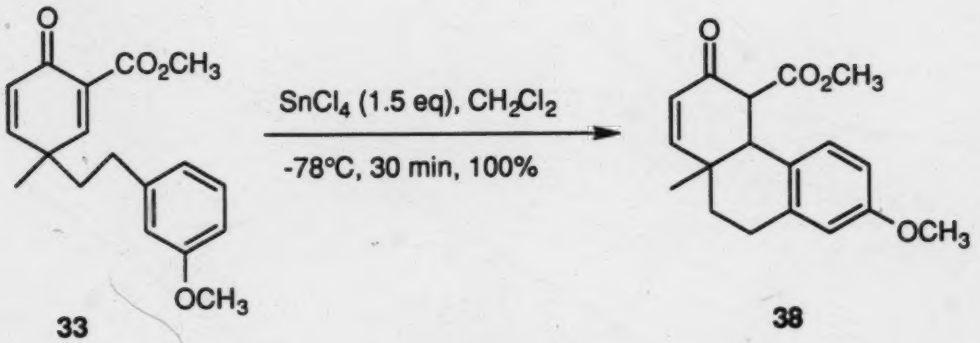
THF providing dialkylated enone **35** in 71% yield over two steps. The high resolution mass spectrum of compound **35** displayed a molecular ion peak at m/z 288.1717 corresponding to the expected formula $C_{18}H_{24}O_3$. The carbonyl absorption band at 1650 cm^{-1} was observed for the enone in the ir spectrum. By analysis of the ^1H nmr spectrum, the vinylic proton of the enone moiety appeared at δ 5.28 as a singlet. The presence of the aromatic protons at δ 7.18 and 6.75, and the methyl singlet at δ 1.17 was evident for the incorporation of the alkylating agents.

To continue the synthesis with compound **35**, three manipulations need to be performed in order to reach the desired keto ester for cyclization. Firstly, compound **35** was subjected to reduction with lithium aluminum hydride providing presumably two epimeric alcohols. This was followed by acid hydrolysis with 10% HCl to afford enone **36** in 88% yield over two operational steps. Enone **36** displayed a carbonyl absorption at 1680 cm^{-1} in its ir spectrum. In the ^1H nmr spectrum, the two vinylic protons of the enone moiety were found at δ 6.75 and 5.92, each as a doublet with a coupling constant of 10.0 Hz, exhibiting the characteristics of the *cis*-disubstituted olefin, whereas an aromatic proton appeared as a doublet of doublets (J = 8, 8 Hz) at δ 7.21 and the other three aromatic protons overlapped at δ 6.75. The high resolution mass spectrum displayed a molecular ion peak at m/z 244.1459, in agreement with the molecular formula $C_{16}H_{20}O_2$ which was also supported by the elemental analysis. Secondly, for further synthetic transformation, it was necessary to introduce the ester moiety into the position alpha to the ketone of the compound, and thus carbomethoxylation of **36** was carried out using dimethyl carbonate and sodium hydride to give keto ester **37** in 95% yield as a

mixture of three isomeric forms from which the enol form was observed to be approximately 15% as indicated by the ^1H nmr spectrum. Its molecular formula was confirmed as $C_{18}H_{22}O_4$ by both the elemental analysis and the high resolution mass spectrum. Finally, to complete the last transformation in which compound **37** could be converted to the required conjugated keto ester **33**, installation of the second double bond must be accomplished. Thus, the method of DDQ oxidation was again employed which was supposedly facilitated by the enol form of the mixture **37** to afford **33** in 98% yield after four hours at room temperature. The regiochemical outcome of this reaction was readily proven by spectroscopic means.

Thus, in the ^1H nmr spectrum, compound **33** displayed the vinylic proton at δ 7.56 as a doublet (J = 3 Hz) belonging to H_3 which was simultaneously deshielded by both ketone and ester functional groups. Two other olefinic protons appeared at δ 6.79 (dd, J = 3, 10 Hz) and δ 6.35 (d, J = 10 Hz), characteristic of *cis*-disubstituted olefin. Also, the aromatic protons were observed at δ 7.17 (dd, J = 8, 8 Hz), 6.72 (dd, J = 2.5, 8 Hz), 6.68 (broad doublet, J = 8 Hz) and 6.63 (broad singlet). The methoxy and methyl singlets were shown at δ 3.86, 3.78 and 1.35, respectively. In addition, the structure of this compound was confirmed by the ^{13}C APT nmr spectrum in which the ketone carbonyl signal was displayed at δ 181.54, whereas the ester carbonyl signal appeared at δ 165.07. The regiochemical integrity of compound **33** was easily ascertained by the ir spectroscopy, which showed the carbonyl absorption bands at 1666 and 1741 cm^{-1} due to the α,β-unsaturated ketone and ester, respectively. Also, its high resolution mass spectrum revealed a molecular ion peak at m/z 300.1355, in agreement with

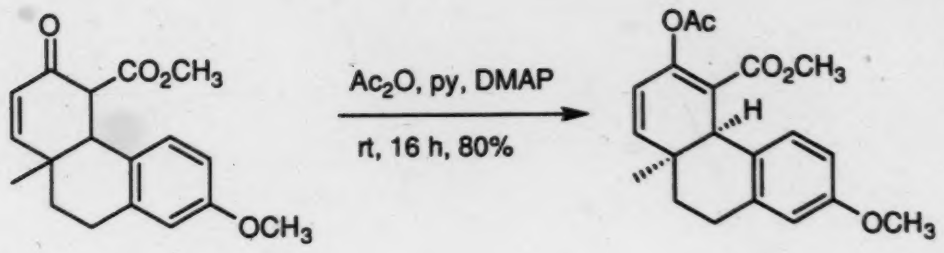
the molecular formula $C_{18}H_{20}O_4$, which was firmly supported by the elemental analysis.



33 **38**

Scheme 25

With enone ester **33** in hand, we went on to examine its cyclization promoted by Lewis acid. As expected, with this compound which contains a methoxy group at the *ortho*/*para* position relative to the site of cyclization and thus exerts greater electron donating effect, the cyclization was extremely facile. As illustrated in Scheme 25, when compound **33** was treated with stannic chloride in dichloromethane, the cyclization occurred rapidly even at -78°C and the desired cyclization product **38** was obtained in quantitative yield after thirty minutes. It existed as an inseparable mixture of two epimers and an enol tautomer in a ratio of 3:3:4, respectively. Interestingly but not surprisingly on steric grounds, the cyclization occurred completely *via* the *para* position relative to the methoxy group. The relative structure of this compound was verified by its converstion to the corresponding enol acetate **39** (Scheme 26), the stereochemistry of which was assigned by spectroscopic means.



38 **39**

Scheme 26

In the ir spectrum, this compound displayed two carbonyl absorption bands at 1765 cm^{-1} (enol acetate) and 1707 cm^{-1} (α,β-conjugated ester). The molecular ion peak in accord with the molecular formula of $C_{20}H_{22}O_5$ was found at m/z 342.1462 in the high resolution mass spectrum, which was in agreement with the elemental analysis. Moreover, compound **39** revealed in the ^{13}C APT nmr spectrum two signals at δ 168.4 and δ 167.0, assigned to the ester carbonyls. Further confirmation of the structure was derived from the ^{1}H nmr spectrum in which a doublet of doublets (J = 1.5, 10 Hz) at δ 6.08 and a doublet (J = 10 Hz) at δ 5.66 were attributed to the vinylic protons, whereas the ring junction proton was substantially shifted downfield to δ 3.79 (a broad singlet) due to the deshielding effects of both conjugated double bond and aromatic ring. A complete set of ^{1}H nmr data is outlined in Table 2 below.

As seen in Figure 4, the ring junction stereochemistry was carefully assigned on the basis of NOE experiments performed on compound **39**, which provided unambiguous stereochemical information. In this regard, irradiation of the angular methyl group caused enhancement in the intensity of the ring junction

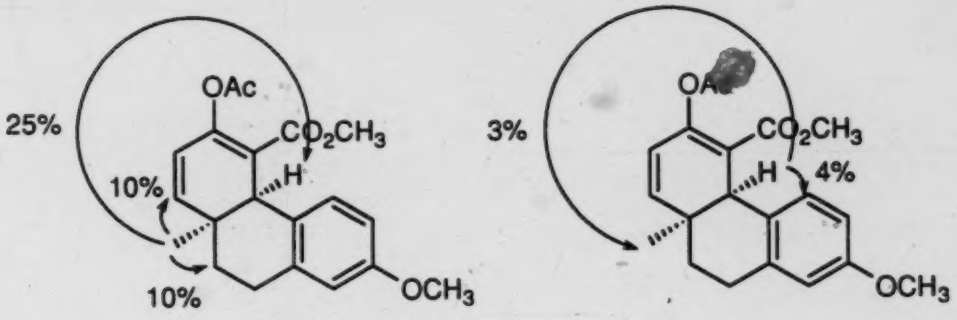
proton (25%), adjacent vinylic proton (10%) and adjacent methylene protons (10%). On the other hand, irradiation of the ring junction proton resulted in enhancements of the angular methyl (3%) and the nearby aromatic proton (4%).

Table 2. ^{1}H nmr data of compound **39**

Proton	**δ** (ppm)	**Multiplicity** (J in Hz)
Ar**H**	6.96	d (J = 8.0)
Ar**H**	6.68	dd (J = 2.5, 8.0)
Ar**H**	6.57	d (J = 2.5)
CH=CHCOAc	6.08	dd (J = 1.5, 10.0)
CH=CHCOAc	5.66	d (J = 10.0)
OCH_3	3.82	s
ring junction **H**	3.79	broad singlet
OCH_3	3.72	s
2 x ArCH_2	2.93-2.68	m
CH_3COO	2.24	s
2 x CH_2	1.98-1.78	m
CH_3	1.23	s

Overall, we have successfully explored the use of the cross conjugated β-keto ester system to facilitate the rapid construction of the highly functionalized hydrophenanthrene ring system which could serve as the nucleus of a large number of naturally occurring compounds.[31]

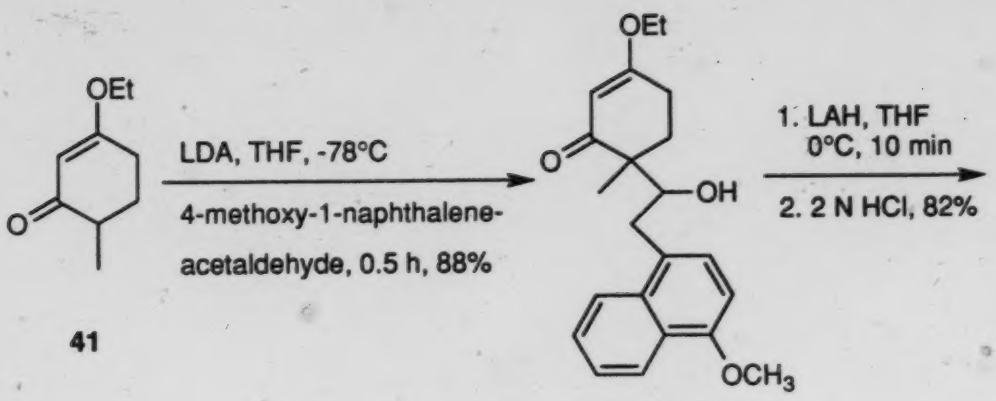
Synthetically, by introducing a suitable aromatic appendage, the above procedure can be conceivably extended to the preparation of compounds containing various numbers of aromatic rings with pre-existing functionalities. As a result, we have turned our attention to the synthesis of tetracyclic compounds, specifically the hydrochrysenes, employing our newly developed methodology. The synthesis was easily achieved as follows.



39 **39**

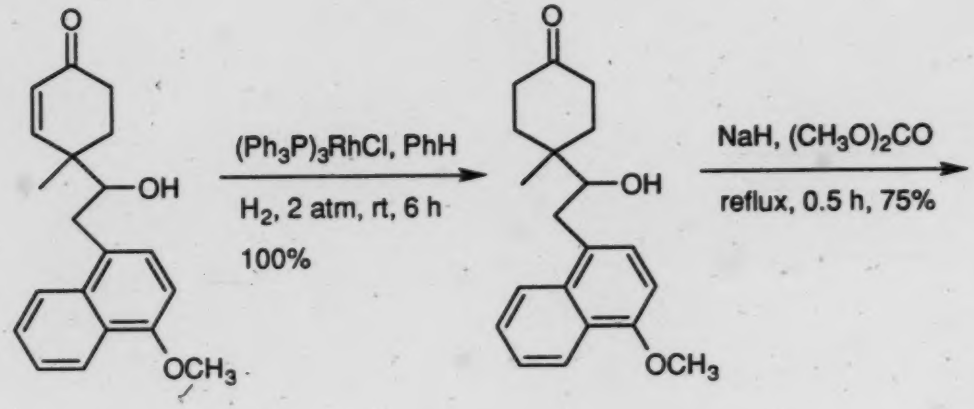
Figure 4

In pursuing this goal, it is necessary to build up the α,β-unsaturated keto ester moiety in compound **40**, a potential intermediate for the cyclization process. Thus, as depicted in Scheme 27, the synthesis commenced with the aldol condensation of 3-ethoxy-6-methyl-2-cyclohexenone **41**[32] and 4-methoxy-1-naphthaleneacetaldehyde, which was prepared in 63% yield from 4-methoxynaphthaldehyde *via* sequential treatment with $Ph_3P{=}CHOCH_3$ in THF at room temperature for 16 hours and 10% hydrochloric acid (Scheme 28), to give an 88% yield of an inseparable mixture of two diastereomeric ketols **42**. The 4-methoxy-1-naphthaleneacetaldehyde above could be alternatively prepared in



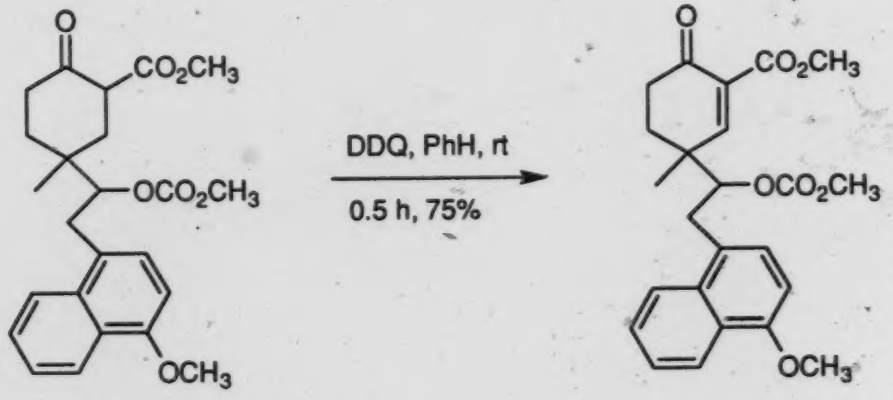
41

42



43

44



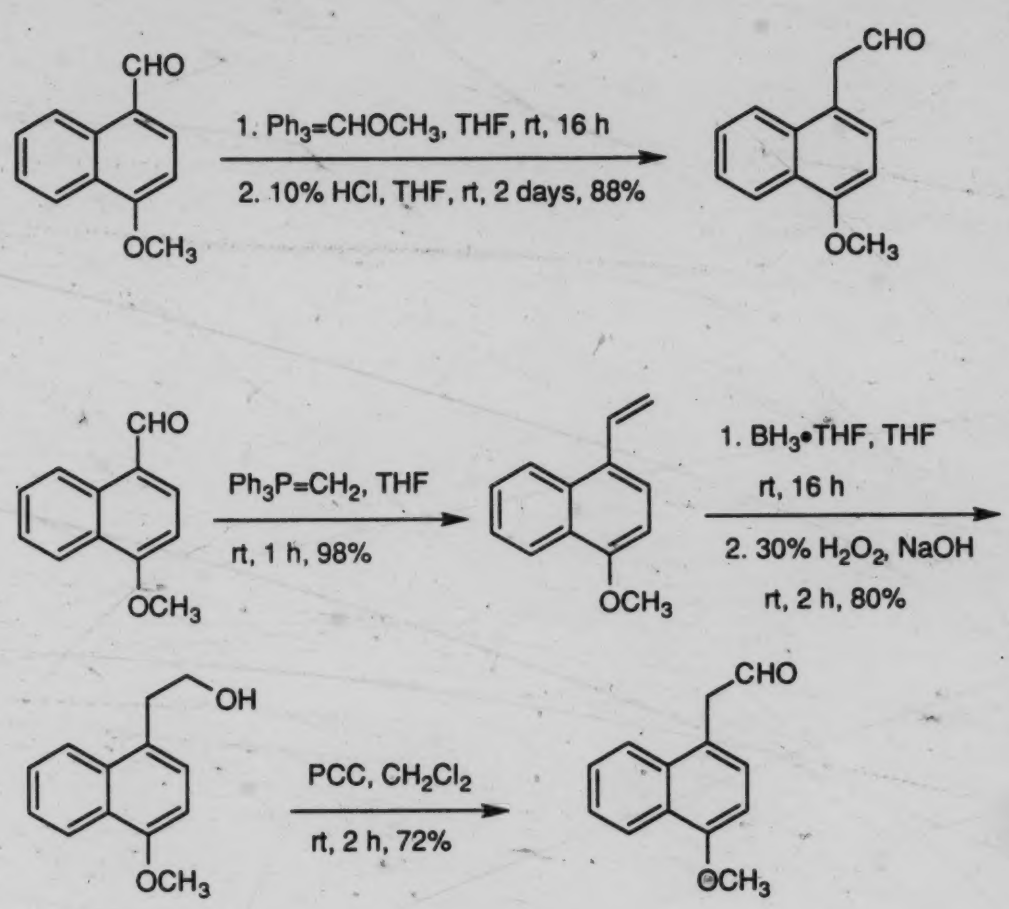
45

40

Scheme 27

an overall yield of 56% through the synthetic sequence as illustrated in Scheme 28. In the aldol reaction, the ratio of the two diastereomers could not be determined since they both displayed unexpectedly overlapped signals in the ^1H nmr spectrum. However, the existence of both isomers was indicated by two different sets of signals in the ^{13}C APT nmr spectrum. Thus, the structure of the major isomer so produced was assigned spectroscopically. In this particular case, the carbonyl was observed in the ^{13}C APT nmr spectrum at δ 205.6 which was atributed to the enone. In addition, a signal at δ 75.5 was indicative of the secondary alcohol moiety. In the ^1H nmr spectrum, the vinylic proton was found as a doublet at δ 5.30 (J = 1 Hz) due to long-range coupling with one of the methylene protons. The proton adjacent to the hydroxyl group appeared at δ 4.19 as a doublet of doublets (J = 2 and 10 Hz), while the methyl group alpha to the ketone was observed at δ 1.32 as a sharp singlet. The presence of the ethoxy group was shown by the signals at δ 3.92 (a quartet, J = 7 Hz, CH_2O-) and δ 1.29 (a triplet, J = 7 Hz, CH_3CH_2O-), whereas the signal at δ 3.98 was attributed to the methoxy group substituted on the phenyl ring. Also, the six aromatic protons were displayed at δ 8.33 (dd, J = 1.5, 8 Hz), 8.14 (broad d, J = 8 Hz), 7.58 (ddd, J = 1.5, 8, 8 Hz), 7.49 (ddd, J = 1.5, 8, 8 Hz), 7.31 (d, J = 8 Hz) and 6.76 (d, J = 8 Hz). The carbonyl band was found at 1605 cm^{-1}, characteristic of the enone in the ir spectrum, whereas the broad absorption band of the hydroxyl group appeared at 3418 cm^{-1}. Furthermore, the high resolution mass spectrometry established the molecular formula as $C_{22}H_{26}O_4$ on the basis of the observed molecular weight of 354.1831.

To continue the synthesis, the ketone group of **42** was reduced to the alcohol level with lithium aluminum hydride in ether at 0°C, which was immediately



Scheme 28

followed by acid hydrolysis affording the enones **43** in 82% yield. Of particular structural diagnosis was the ir absorption at 1672 cm^{-1}, characteristic of enone carbonyl group, and a broad band absorbed at 3426 cm^{-1} exhibited the existence of the hydroxyl functionality. In the ^1H nmr spectrum, compounds **43** showed two signals at δ 7.04 and 6.01 with the same coupling constant (J = 10 Hz), ascribed to the protons of the conjugated *cis*-disubstituted olefin. And the disappearance of the signals at δ 3.92 and 1.39 shown in the ^1H nmr spectrum

of the starting material, suggested the detachment of the ethoxy group. Furthermore, the high resolution mass spectrum showed the molecular ion peak at m/z 310.1585, entirely consistent with the formula $C_{20}H_{22}O_3$.

As previously observed, the directing nature of the methoxy group in compound **18**, in which case the methoxy group was substituted at the *meta* position relative to the potential site of cyclization, was not efficient to facilitate the cyclization of the precursor **18**, and thus resulted in the competitive rearrangement process leading to the aromatization products. However, this difficulty was circumvented by the removal of the existing double bond in compound **23** and thus suppressed the migration process of the side chains when **18** was treated with Lewis acid.

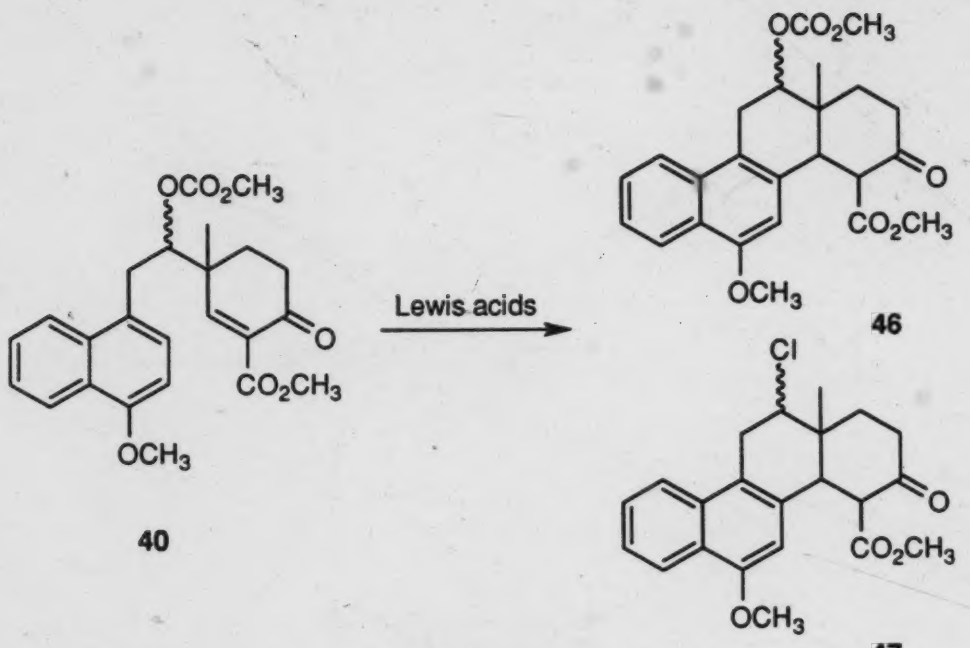
Based on this analogy, to effectively facilitate the construction of chrysene carbon skeleton, it is plausible to eliminate the double bond in compounds **43**. To accomplish this, compounds **43** were subjected to catalytic hydrogenation using Wilkinson's catalyst to furnish the saturated ketones **44** in quantitative yield. Evidence for the structure **44** was derived from the ^1H nmr spectrum, which showed the absence of the olefinic protons, but instead displayed a more complex signal pattern in the methylene region. In supporting the structural analysis of compounds **44**, the ir spectrum revealed an absorption band at 1711 cm^{-1}, characteristic of a saturated ketone. In addition, its high resolution mass spectrum showed a molecular ion peak at m/z 312.1732, consonant with the formula $C_{20}H_{24}O_3$.

With ample quantities of compounds **44** available, its further transformations to the desired conjugated keto esters **40** were examined. It was envisioned at this stage that the installation of the methyl ester functionality to the position alpha to the ketone was necessary. Bearing this idea in mind, compounds **44** was subjected to carbomethoxylation using sodium hydride and dimethyl carbonate under reflux and resulted in the β-keto ester moiety in compounds **45** with concomitant protection of the alcohol in the form of a carbonate. From the analysis of ^1H nmr spectrum, compounds **45** thus formed in 75% yield existed mostly in its enol form. In this fashion, compounds **45** showed a sharp singlet at δ 12.18 for the enol hydrogen, whereas three singlets appeared at δ 3.98, 3.77 and 3.39 belonging to the three OCH_3 groups. In addition, the absence of the hydroxyl group was evident in the infrared spectrum which was replaced by a carbonate functionality displaying an absorption band at 1746 cm^{-1}. Further structural confirmation was obtained by the analysis of high resolution mass spectrum which showed the molecular ion peak at m/z 428.1836 corresponding to molecular formula $C_{24}H_{28}O_7$.

For further synthetic manipulation directed toward the elaboration of **40**, it appeared most appealing to selectively introduce the double bond into the structure to generate the conjugated β-keto ester system. Since compounds **45** possessed a high degree of enolization, which was required for effective DDQ oxidation, it would be a desirable precursor for the synthesis of compounds **40**. As anticipated, treatment of compounds **45** with DDQ in benzene at room temperature provided two inseparable diastereomeric enone esters **40** in a 6:1 ratio (based on ^1H nmr analysis) and 75% combined yield. Since these two diastereomers displayed an almost identical set of signals in the ^1H nmr

spectrum, the structural analysis of the major isomer would be a representative. Accordingly, the major isomer of **40** displayed a sharp singlet at δ 7.45 for the vinylic proton in the ^{1}H nmr spectrum whereas the three sharp singlets were observed at δ 4.00, 3.75 and 3.45 for the three OCH_3 groups present in the compound. Moreover, six protons were found in the region between δ 8.30 and 6.70, assigned to the aromatic protons of the side chain, and a sharp singlet appeared at δ 1.41, indicative of the methyl group. Interestingly, the two diastereomers **40** revealed a single set of signals in the ^{13}C APT nmr spectrum with a total of twenty four carbons required for the carbon skeleton of enone esters **40**, of which the three signals at δ 193.7, 166.2 and 164.8 accounted for the carbonyl functionality of ketone, ester and carbonate, respectively. In the high resolution mass spectrum, compounds **40** showed a molecular ion peak at m/z 426.1677, which was consistent with the molecular formula $C_{24}H_{26}O_7$. Also, its ir spectrum portrayed the enone moiety at 1658 cm^{-1} and the ester character at 1747 cm^{-1}.

Having achieved the proper functionalization of the cyclization precursors **40** in a reasonably short manner, we were now ready to explore its cyclization mode. If successful, this annulation would represent another method for the construction of hydrochrysene carbon skeleton. Interestingly, when compounds **40** were treated with stannic chloride in dichloromethane at room temperature for one day, carbonates **46** and the corresponding chlorides **47** were formed in equal amount (Scheme 29). Mechanistically, the halide formation in compounds **47** is, though unusual due to the stability of the carbonate function, the result of the coordination of stannic chloride with the oxygen of the carbonate moiety, followed by the replacement of the carbonate functionality



40 46 47

Scheme 29

Table 3. Cyclization of compounds **40** under Lewis acid catalysis

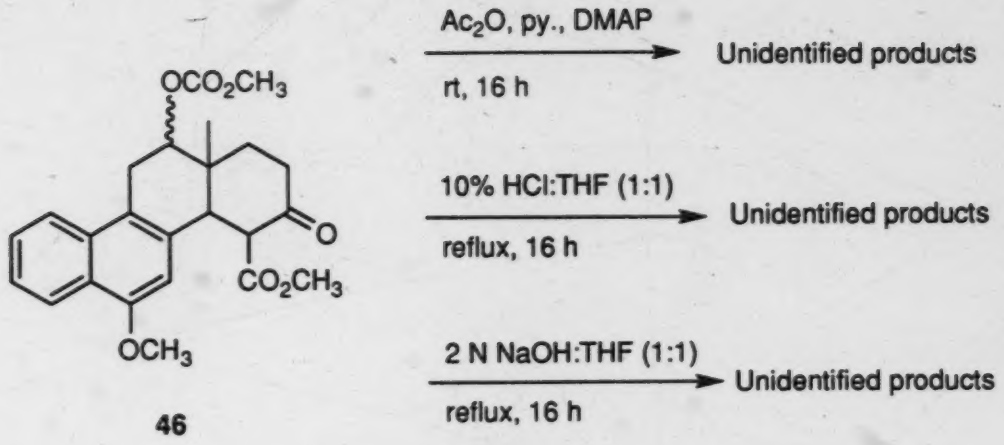
Lewis acids	Solvents	Temp.	Time	Yield of 46	Yield of 47
$SnCl_4$	CH_2Cl_2	room temp.	1 day	49%	43%
$AlCl_3$	Et_2O	room temp.	2 h	95%	0%

with the chlorine atom. The presence of the chlorine atom was firmly supported by mass spectral data, which revealed a cluster of molecular ions due to the presence of the two chlorine isotopes (^{37}Cl, ^{35}Cl). The most abundant or base

peak (^{35}Cl) was observed at m/z 386.1288, which corresponded to the molecular formula $C_{22}H_{23}O_4Cl$.

On the other hand, when the reaction was carried out in ether at room temperature using aluminum chloride as the Lewis acid, the highly functionalized hydrochrysene carbonates **46** were obtained as the sole products in virtually quantitative yield after 2 hours (Table 3). These carbonates were found mostly in their enol forms and remained in a ratio of 6:1, as indicated by the ^1H nmr spectrum, which showed a sharp singlet at δ 12.63 for the enol proton of the major isomer. The signals of the three OCH_3 groups were observed as singlets at δ 3.92, 3.89 and 3.77, whereas the ring junction proton appeared at δ 4.08 also as a singlet. In its mass spectrum, the carbonates showed a molecular weight of 426.1673 consistent with the molecular formula $C_{24}H_{26}O_7$. From the cleanliness of ^1H nmr spectrum, we suspected that the cyclization occurred to produce a *cis* fusion. However, proof was required to confirm this evidence, and it was not possible to use spectroscopic methods profitably for the stereochemical analysis of **46**. Thus, the structure and ring junction stereochemistry of compounds **46** were retrieved from spectroscopic analysis performed on a derivative of these keto esters.

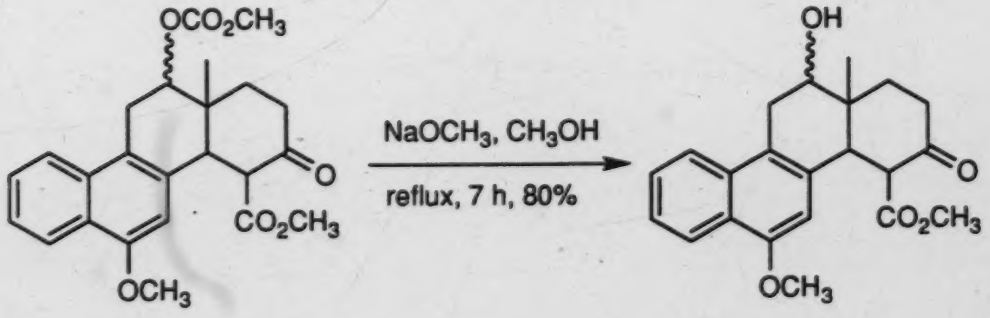
The first solution that comes immediately to mind in order to accomplish this ultimate goal is to acetylate the mixture **46** hoping that we can separate the two diastereomers. Unfortunately, when compounds **46** were exposed to acetic anhydride in pyridine with a catalytic amount of dimethylaminopyridine, a mixture of unidentified products was detected (Scheme 30). Attention was then



46

Scheme 30

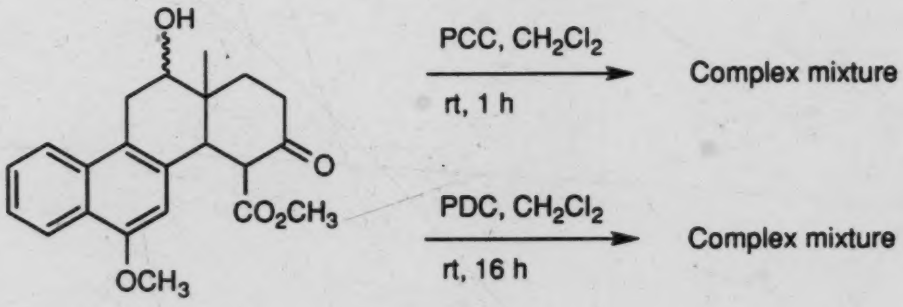
turned to direct destruction of the keto ester moiety in order to simplify structural studies of compounds **46**. In attempts to remove the ester group, both acid and base hydrolyses were perfomed; however, they both provided a complicated mixture of compounds. These failures could be attributed to the high level of functionalization of **46**. At this point, an appealing alternative by-passing the



46 **48**

Scheme 31

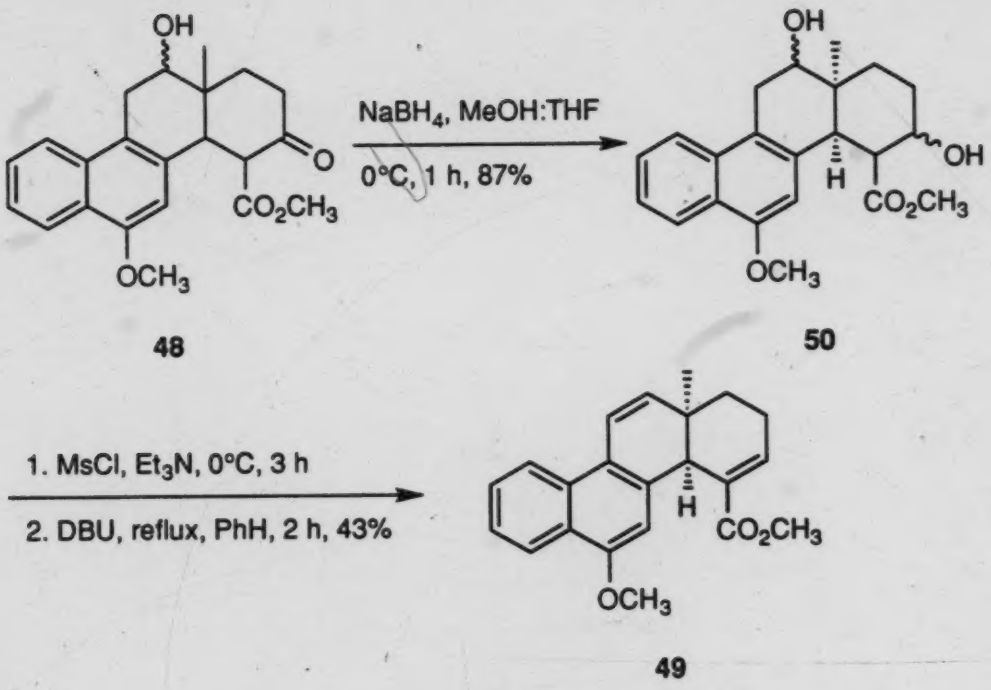
above difficulties would be elimination of the asymmetry of the carbonate substituted carbon. In this regard, compounds **46** were treated with sodium methoxide in refluxing methanol for seven hours, providing the corresponding alcohols **48** in 80% yield (Scheme 31). These alcohols displayed one OCH_3 group less, suggesting that the carbonate group was hydrolyzed. In addition, its ir spectrum showed a broad absorption band at 3457 cm^{-1}, indicative of the hydroxyl functionality. The structure of compounds **48** were further verified by high resolution mass spectrum which revealed the molecular ion peak as the base peak at m/z 368.1626, completely in agreement with the molecular formula $C_{22}H_{24}O_5$.



48

Scheme 32

However, attempted oxidation of alcohols **48** with pyridinium chlorochromate (PCC) in dichloromethane afforded complex mixtures of unidentified products (Scheme 32). Similarly, alcohols **48** obtained above also failed to give the corresponding ketones when exposed to pyridinium dichromate (PDC). Frustrated by the lack of success in this area, we deemed it necessary to devise an alternative solution. In order to examine the stereochemistry of the ring



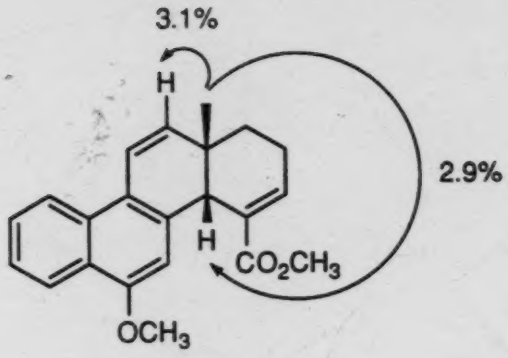
48 **50** **49**

Scheme 33

junction, the design of analog **49** came across our mind, which involved three chemical transformations from **48**. The synthesis began with a modification of the β-keto ester moiety. Conversion of the β-keto ester into β-hydroxy ester was carried out effectively using sodium borohydride in methanol and THF (1:1) at 0°C for one hour leading to a mixture of four diastereomeric isomers **50** (Scheme 33), the structures of which were deduced by spectroscopic methods. To continue the synthesis with **50**, two manipulations need to be performed. Firstly, the diols must be converted to good leaving groups and secondly, the elimination has to be effectively facilitated to provide the desired olefins. Bearing this idea in mind, reaction of diol esters **50** with methanesulfonyl chloride and triethylamine at 0°C afforded the corresponding mesylates which

were treated immediately, without purification, with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene to provide the desired compound **49** in 43% yield over two steps. With the single isomer **49** in hand, we can examine the ring junction stereochemistry of the hydrochrysene derevatives obtained from the cyclization, based on spectroscopic analysis performed on **49**. As anticipated, compound **49** displayed a carbonyl absorption band at 1716 cm^{-1}, characteristic of an α,β-unsaturated ester. Formation of the double bonds was confirmed by the ^1H nmr spectrum which displayed two doublets at δ 7.13 and 5.79 with the same coupling constant (J = 10 Hz), indicative of *cis*-disubstituted olefin, and a doublet of doublets at δ 7.07 for the vinylic proton of the α,β-unsaturated ester moiety. The angular methyl group appeared at δ 1.14 as a sharp singlet, whereas the ring junction proton was observed as a broad singlet at δ 3.88. Along with the six aromatic protons in the region between δ 8.30 and 6.50, a sharp singlet was found at δ 3.93 accounting for OCH_3 of the methyl ether, and the presence of the methyl ester was verified by a sharp singlet at δ 3.72. The structural diagnosis of ester **49** was further supported by the high resolution mass spectroscopy which established the molecular weight of 334.1565 corresponding to the expected molecular formula $C_{22}H_{22}O_3$. The stereochemistry at the ring junction was readily elucidated by NOE experiment.

As shown in Figure 5, irradiation of the angular methyl at δ 1.14 resulted in enhancements of ring junction proton (2.9%) and the adjacent vinylic proton (3.1%). It provided proof for the *cis* ring junction of the products formed from the cyclization.



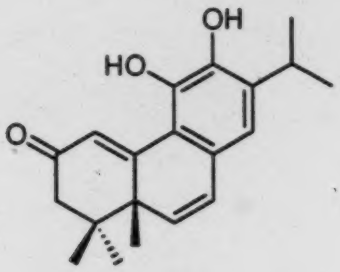
49

Figure 5

In conclusion, the results described above illustrated that the conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclization, which occurred readily with regio- and stereoselectivity. This cyclization process allows for expeditious construction of a variety of polycyclic ring systems such as hydrophenanthrene and hydrochrysene with a high degree of functionalization. It is expected to have broad utility in the synthesis of polycyclic natural products. As a result, the above newly developed methodology has prompted us to undertake the synthetic studies towards the total synthesis of pygmaeocin C (**51**) (Figure 6).

In addition to several other diterpenoids, pygmaeocin C was first isolated in 1990 from the roots of *Pygmaeopremna herbacea*, a small shrub growing in the Yunnan and the Hainan provinces of China and also in the northern part of India.[33] Although the roots of *Pygmaeopremna herbacea* are used in Yunnan as a folk medicine against inflammation and malaria, the biological activity of

this particular natural product remains unknown and further investigation into this area is required.



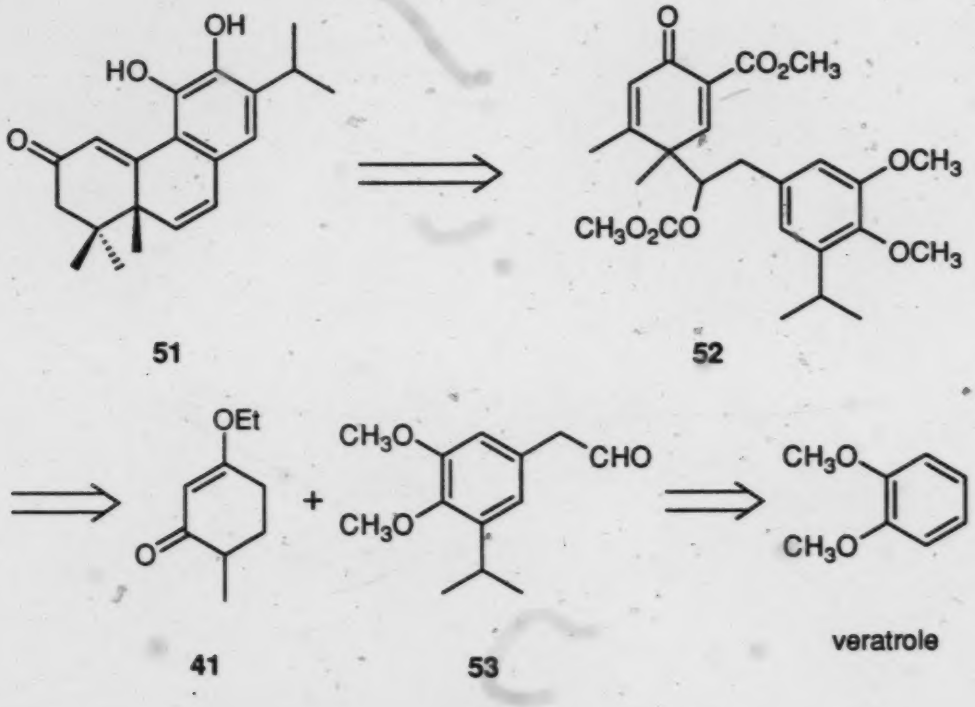
51

Figure 6

Pygmaeocin C was obtained as a yellow foam, and the structure was elucidated on the basis of spectroscopic data, whereas the absolute configuration was assigned tentatively on the basis of a biogenetic pathway.[33] Its high resolution mass spectrum showed the molecular ion peak at m/z 312.1722 for $C_{20}H_{24}O_3$. In the infrared spectrum, the carbonyl absorption band was observed at 1630 cm^{-1}, whereas the hydroxyl groups displayed their absorptions at 3500 cm^{-1}. Structural confirmation of pygmaeocin C was further established by nmr spectroscopy.[33] Nevertheless, the absolute configuration of the methyl group (C_{20}) was established indirectly as β-configuration in this particular diterpenoid by the biogenetical interrelation with the co-occurring diterpenoid sugiol in the same plant.[33]

To the best of our knowledge, since its isolation, there has never been any total synthesis of this natural product. Inspired by our observations on the newly

developed intramolecular Friedel-Crafts alkylation promoted by the conjugated β-keto ester system, a retro-synthetic scheme of the total synthesis of pygmaeocin C (**51**) was developed in our laboratory to demonstrate the synthetic utility of this methodology as outlined in Scheme 34. In this strategy, the key operation is the rapid construction of the hydrophenanthrene ring system *via* the polyene cyclization of the suitable intermediate **52**. Attempts to synthesize the keto ester **52** was made and the preliminary studies are discussed as follows.



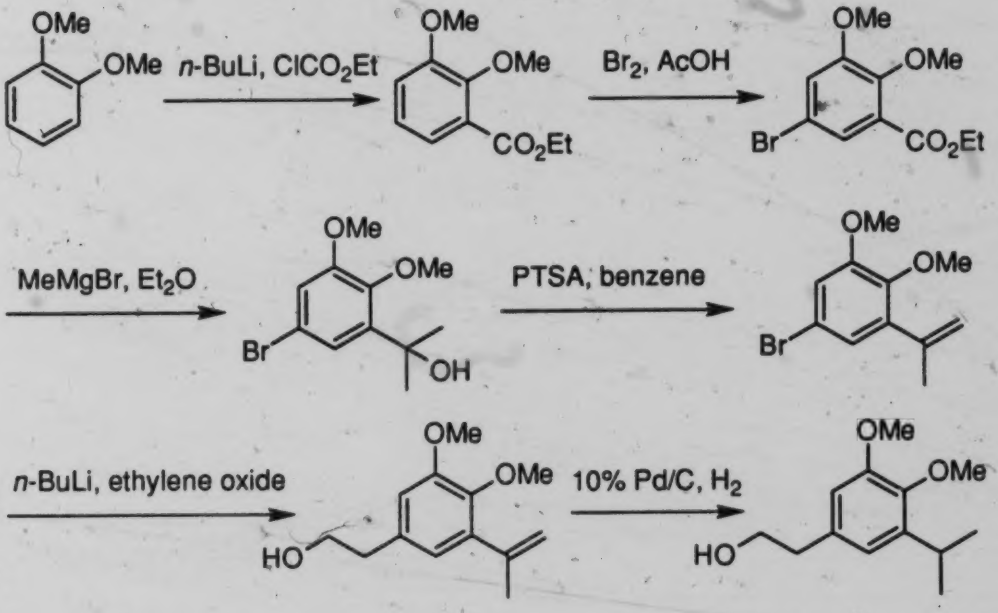
51 **52**

41 **53** veratrole

Scheme 34

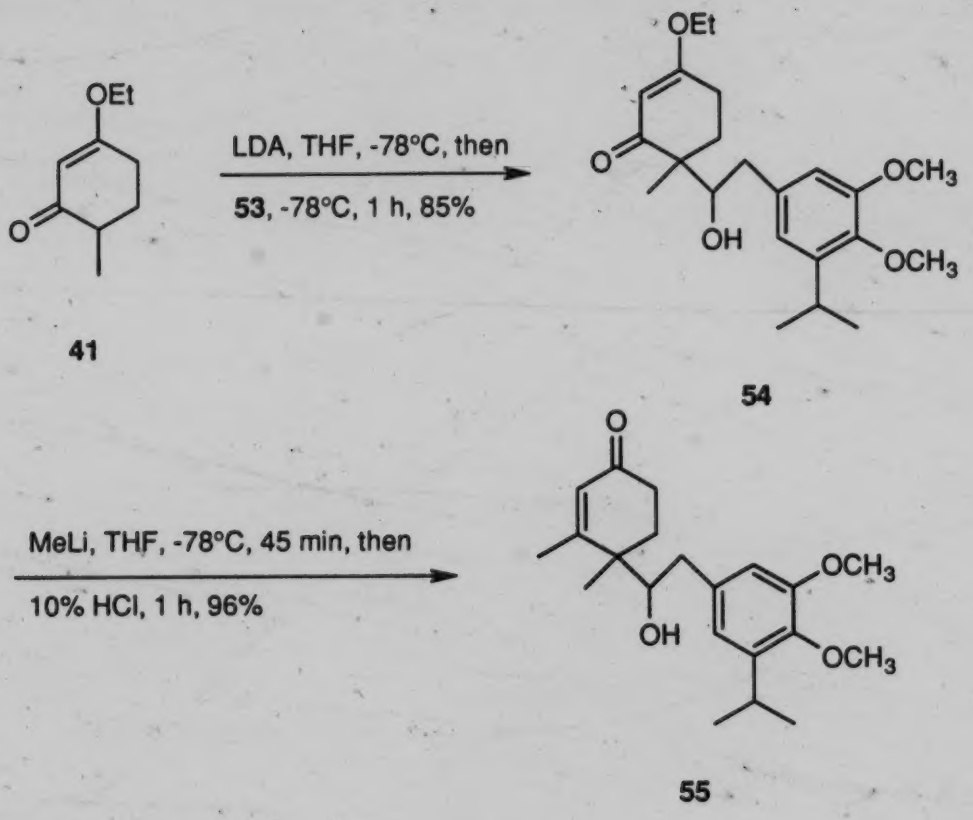
As illustrated in the retro-synthetic Scheme 34, compound **52** was envisioned as a desirable precursor because it contained appropriate functionalities which

could, in principle, be transformed to **51**. Aldehyde **53** was readily obtained in 91% yield when its corresponding alcohol was treated with PCC in dichloromethane at room temperature for 1.5 hours. A literature search revealed that the requisite alcohol had been prepared in five steps starting from the commercially available veratrole by Wang and coworkers in 1996 as illustrated in Scheme 35.[34]



Scheme 35

With the aldehyde **53** in hand, the synthesis of compounds **54** was effected at low temperature by condensing this aldehyde with the known enone **41** (Scheme 36). This gave compounds **54** in 85% yield as an inseparable mixture of two diastereomeric isomers in a ratio of 3:1. In the ir spectrum, the carbonyl absorption band was shown at 1643 cm^{-1} for the enone, whereas the

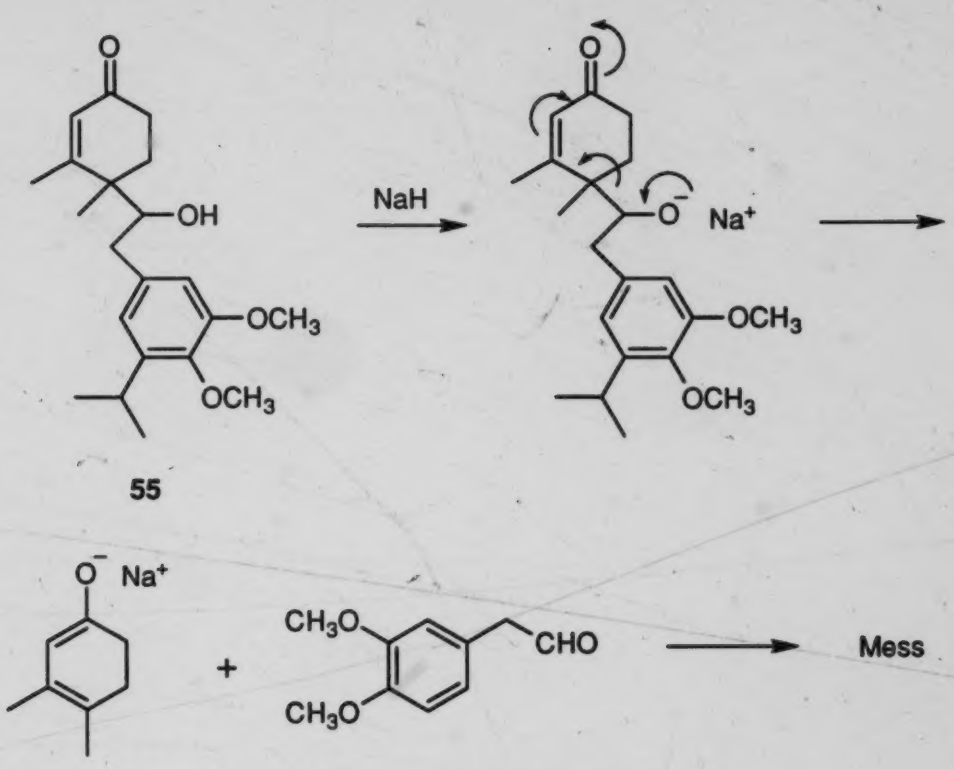


Scheme 36

hydroxyl group displayed an absorption band at 3430 cm^{-1}. In the high resolution mass spectrum, the molecular ion peak was found at m/z 376.2245 which was consistent with the molecular formula $C_{22}H_{32}O_5$. For the major isomer of **54**, the ^1H nmr spectrum revealed two doublets at δ 6.68 and 6.67 with the same coupling constant (J = 2 Hz) accounting for the two aromatic protons with a *meta* relationship. The two OCH_3 groups were found at δ 3.84 and 3.77, each as a sharp singlet, whereas a sharp singlet was detected at δ 1.23 for the quarternary methyl group. In addition, the vinylic proton was observed as a doublet at δ 5.25 with a coupling constant about 1 Hz, due to

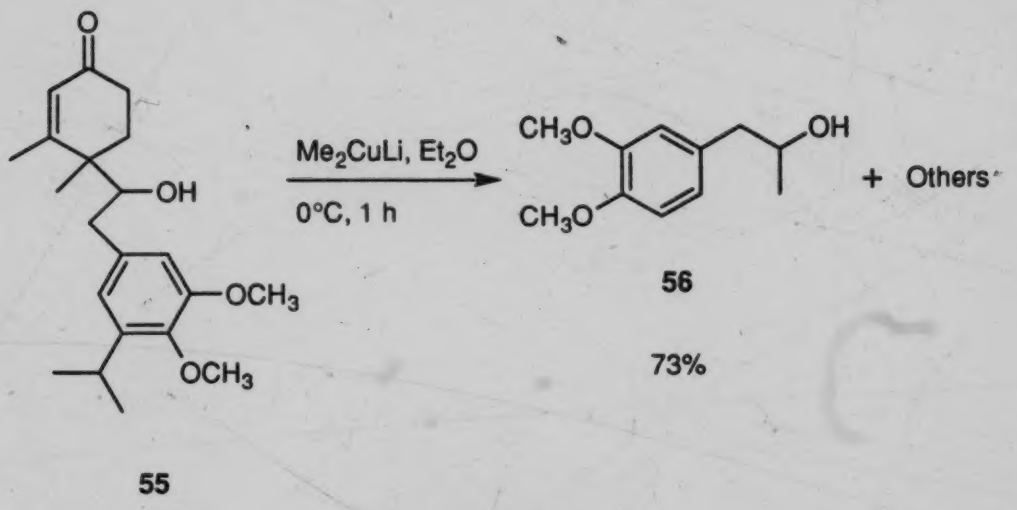
long-ranged coupling with one of the methylene protons. For the minor isomer, the attachment of the aromatic side chain was also evident by the presence of the two aromatic protons which displayed two doublets at δ 6.66 and 6.64 with the same coupling constant (J = 2 Hz). Also, the proton adjacent to the hydroxyl group showed a doublet of doublets at δ 4.02 (J = 2.5, 10 Hz). The vinylic proton was observed as a doublet (J = 1 Hz) at δ 5.30. Interestingly but not surprisingly, the ^{13}C APT nmr spectrum of the mixture **54** displayed two distinguished sets of signals, of which two signals at δ 206.0 and 204.3 were observed for two carbonyl groups whereas two signals at δ 76.8 and 76.3 were attributed to the hydroxyl-bearing carbons in the two isomers.

To continue the synthesis of **52**, compounds **54** was subjected to 1,2-addition with methyllithium, followed immediately by hydrolysis with 10% HCl to give enones **55** in 96% yield over two steps. The ir spectrum of this diastereomeric mixture showed a carbonyl absorption band at 1666 cm^{-1} and an absorption band for the hydroxyl group at 3431 cm^{-1}. In the high resolution mass spectrum, the molecular ion peak was shown at m/z 346.2147, in agreement with the required formula $C_{21}H_{30}O_4$. In contrast with that of compounds **54**, the ^1H nmr spectrum of **55** displayed only a single set of signals of which two aromatic protons appeared at δ 6.46 and 6.59, both as a doublet with the same coupling constant (J = 2 Hz). The vinylic proton was found at δ 5.95 as a doublet which had a small coupling (J = 1 Hz) with the nearby vinylic methyl group at δ 2.06. Moreover, two OCH_3 groups were evident by two sharp singlets at δ 3.86 and 3.80. The proton adjacent to the hydroxyl group appeared at δ 3.94 as a broad doublet (J = 10.5 Hz), whereas a sharp singlet at δ 1.32 belonged to the quarternary methyl group.



Scheme 37

In order to introduce the ester moiety into the structure, compounds **55** were exposed to sodium hydride in refluxing dimethyl carbonate. Unexpectedly, the reaction produced a complex mixture of unidentified products. Based on this observation, it could be rationalized that compounds **55** could easily undergo retro-aldol type rearrangement once the corresponding alkoxide ion was generated by a strong base (Scheme 37). Thus, attention was focussed on the removal of the conjugated double bond using lithium dimethylcuprate (Me_2CuLi). However, when mixture **55** was treated with Me_2CuLi in ether at 0°C for one hour, a mixture of compounds was obtained, one of which was verified as compound **56** (Scheme 38). This compound so obtained in 73%



55

56

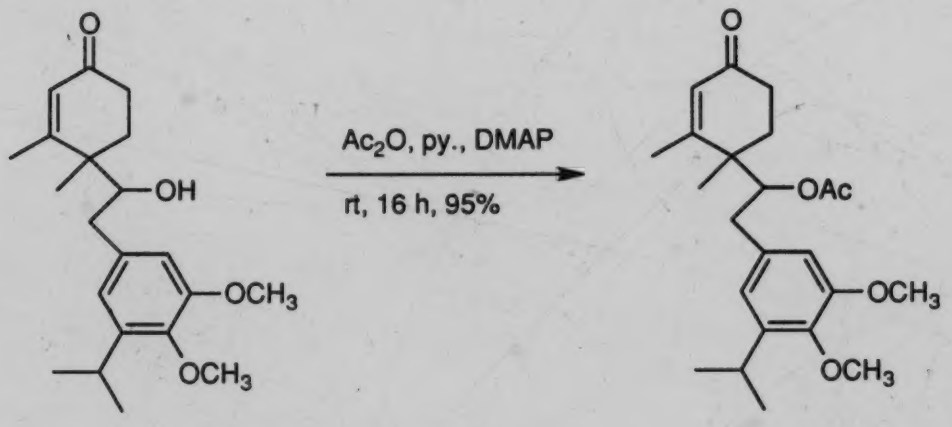
73%

Scheme 38

yield was formed sequentially from retro-aldol rearrangement and 1,2-addition. At this stage, we realized that it was necessary to protect the hydroxyl functionality. To do this, alcohols **55** were treated with acetic anhydride and pyridine with a catalytic amount of dimethylaminopyridine. After sixteen hours at room temperature, the acetate derivatives **57** were produced in virtually quantitative yield as illustrated in Scheme 39. The structural outcome of the acetylation reaction was readily proven by spectroscopic means.

Its mass spectrum depicted a molecular ion peak at m/z 388.2254 corresponding to the expected formula $C_{23}H_{32}O_5$. Two carbonyl absorption bands at 1743 and 1674 cm^{-1} were observed in the ir spectrum whereas there was no indication of the hydroxyl functionality. Also, the ^{13}C APT nmr spectrum showed only a single set of a total of twenty-three carbons for the mixture in which two carbonyl signals at δ 198.5 and 170.0 were observed for the enone

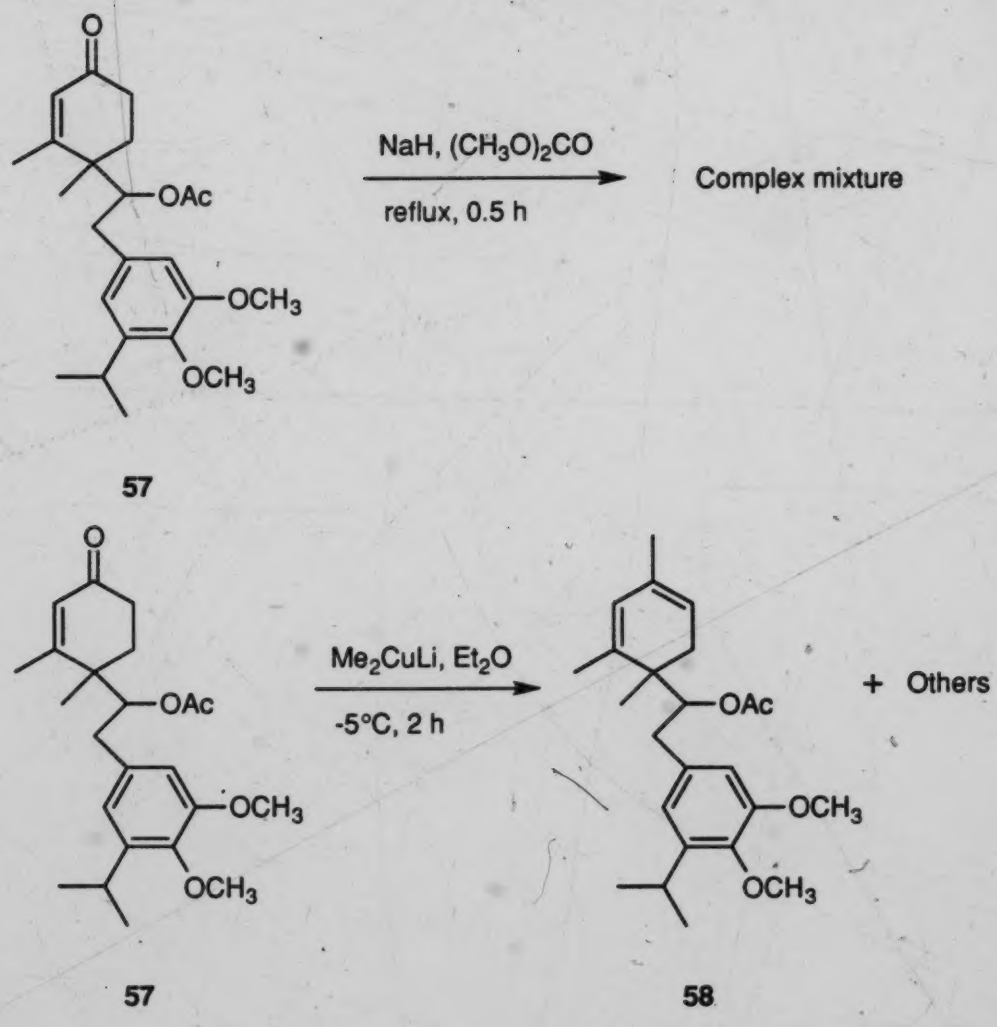
and acetate, respectively. By first order analysis of the ^1H nmr spectrum, two aromatic protons appeared at δ 6.59 and 6.53, each as a doublet with the same coupling constant (J = 2 Hz), whereas the vinylic proton was found also as a doublet (J = 1 Hz) at δ 5.91, due to long-ranged coupling with the vinylic methyl group. As anticipated, the methine proton underwent a downfield shift upon acetylation to δ 5.49 in the ^1H nmr spectrum. All of the above spectral data clearly indicate that the hydroxyl group has been protected as an acetate moiety.



55 **57**

Scheme 39

To continue the synthesis with **57**, attempted carbomethoxylation with sodium hydride and dimethyl carbonate was performed to introduce the ester moiety. However, the reaction provided a mixture of unidentified compounds. Presumably, the methoxide ion, once formed from carbomethoxylation reaction, hydrolyzed the acetate functional group under refluxing condition, leading to retro-aldol rearrangement (Scheme 40). Being incapable of eliciting the



Scheme 40

desired carbomethoxylation reaction, attention was then turned to direct 1,4 addition. Unfortunately, addition of lithium dimethylcuprate (Me_2CuLi) to **57** at -5°C for two hours resulted in the formation of a complex mixture of products, of which the major compound was identified as **58**. Apparently, due to the bulkiness of the side chain, α,β-unsaturated ketones **57** showed a marked

propensity to undergo 1,2-addition with the organolithium compound (Scheme 40).

From the above drawbacks, it is realized that a different carbomethoxylation procedure has to be applied utilizing milder conditions, such as the combination of lithium diisopropylamide and methyl cyanoformate.[35] It is also possible that variation of the conditions for 1,4 addition such as addition of R_3SiX can conceivably lead to successful functional transformations. These possibilities constitute our synthetic efforts currently underway towards the total synthesis of pygmaeocin C **51**.

Experimental

General

Melting points were recorded on a Kofler hot stage apparatus and are not corrected. Combustion elemental analyses were performed by the microanalytical laboratory of this department. Fourier transform infrared spectra were recorded on a Nicolet 7199 or Nicolet MX-1 FTIR spectrophotometer. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on a Bruker WH-200, Bruker AM-300, Bruker WH-400 or Bruker AM-400 spectrometer using deuterochloroform ($CDCl_3$) as solvent unless otherwise stated. Tetramethylsilane (TMS) was used as an internal reference. Coupling constants are reported to ± 0.5 Hz. Chemical shift measurements are reported in ppm downfield from TMS in delta (δ) units. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Carbon-13 nuclear magnetic resonance (^{13}C nmr) spectra were recorded on a Varian UNITY-500 (125 MHz) spectrometer or a Bruker AM-300 (75 MHz) spectrometer, and were obtained as solutions in deuterochloroform as the internal standard setting the central peak at 77.00 ppm. Cabon-13 multiplicities were derived from Carr-Purcell-Meiboom-Gill spin echo *J*-modulated experiments (APT or Attached Proton Test). Methyl and methine groups are shown as signals possessing an antiphase (a) with respect to the deuterochloroform signal, whereas methylene groups, quaternary carbons and carbonyl groups appear in phase (p) with it. Nuclear Overhauser Enhancement (NOE) experiments were determined in the difference mode in which a control

(undecoupled) spectrum was computer substracted from the irradiated spectrum after Fourier transformation. Positive enhancements are defined as signals possessing an antiphase with respect to the irradiated signal. Samples for NOE measurements were deoxygenated with argon for 10 min prior to use. High resolution electron impact mass spectra (hrms) were recorded using an A.E.I. model MS-50 mass spectrometer. Spectral data are reported as m/z values. Bulb-to-bulb distillation was performed using a Kugelrohr distillation apparatus. X-ray analyses were performed by the structure determination laboratory of this department. Concentrations of solvent systems used in column chromatography are given by volumes, e.g., ethyl acetate/hexane (20:80) means 20 parts of ethyl acetate by volume to 80 parts of hexane by volume.

Materials

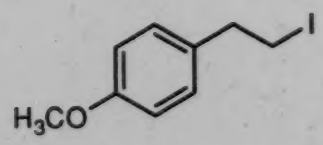
Unless otherwise stated, all materials used are commercially available. All compounds made are racemic. All reactions were carried out under a positive pressure of argon. Solvents were distilled under argon from appropriate drying agents before use. Tetrahydrofuran (THF), diethyl ether and toluene were freshly distilled from a blue or purple solution of sodium benzophenone ketyl. Diisopropylamine was obtained by distillation from sodium hydroxide, potassium hydroxide or calcium hydride. Pyridine, benzene, dichloromethane and triethylamine (TEA) were distilled from calcium hydride. Reactions requiring anhydrous conditions were performed using oven or flame-dried glassware, assembled and allowed to cool while being purged with argon. Argon was passed through a column of 4 A molecular sieves, with a self-

indicating silica gel (coarse grained) as the indicator. Flash chromatography was used routinely for purification and separation of product mixtures, using silica gel (Merck) of 230-400 mesh. All solvents were distilled prior to use for chromatography. Analytical thin layer chromatography (TLC) was carried out on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F254 (E. Merch, Darmstadt). Ultraviolet active materials were detected by visualization under a uv lamp (254 or 350 nm). For TLC, the visualization of the chromatograms was completed by dipping in an ethanol solution of vanillin (5%, W/V) and sulfuric acid (5%, v/v), followed by careful charring on a hot plate.

General Procedure for the Conversion of Alcohols to Corresponding Iodides

To a solution of carbon tetraiodide (2.58 g, 4.97 mmol) in dry dichloromethane (10 mL) at 0°C, was added triphenylphosphine (1.63 g, 6.21 mmol). The mixture was stirred at 0°C for 30 min. The alcohol (630 mg, 4.14 mmol) in dichloromethane (2 mL) was then added. The resulting mixture was allowed to warm up to room temperature. After being stirred vigorously for 30 min, the mixture was allowed to pass through a column of silica gel, eluting with hexanes, to remove the undesired by-products.

2-(*p*-Methoxyphenyl)ethyl Iodide (20)



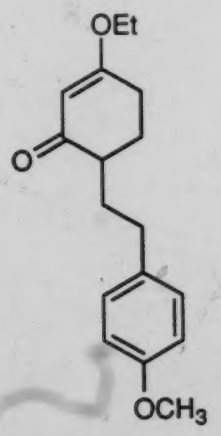
Using the above general procedure, 2-(*p*-methoxyphenyl)ethanol (630 mg, 4.14 mmol) was treated with carbon tetraiodide (2.58 g, 4.97 mmol) and triphenylphosphine (1.63 g, 6.21 mmol) in dry dichloromethane to afford iodide **20** (981 mg, 91%): ir ($CHCl_3$ cast) 2998, 1611 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.12 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.86 (2H, d, J = 9 Hz, 2 x Ar**H**), 3.81 (3H, s, -OC**H**$_3$), 3.32 (2H, t, J = 8 Hz, -C**H**$_2$I), 3.12 (2H, t, J = 8 Hz, ArC**H**$_2$-); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 158.6 (p), 132.9 (p), 129.4 (a), 114.1 (a), 55.3 (a), 39.6 (p), 6.4 (p); hrms M^+ 261.9856 (calcd. for $C_9H_{11}OI$: 261.9855).

General Procedure for Alkylation Using LDA

At 0°C, to a stirred solution of diisopropylamine (1.67 mL, 11.90 mmol) in anhydrous tetrahydrofuran (20 mL), was added dropwise a solution of *n*-butyllithium in *n*-hexane (2.5 M, 3.57 mL, 8.93 mmol). The resulting mixture was stirred for 15 min at 0°C and then cooled to -78°C. A solution of 3-ethoxy-2-cyclohexenone **19** (830 mg, 5.95 mmol) in tetrahydrofuran (2 mL) was added dropwise and the reaction mixture was stirred for 40 min at -78°C. A yellow solution of iodide (5.15 g, 23.8 mmol) in tetrahydrofuran (5 mL) was added dropwise by a syringe to the above lithium enolate solution with stirring. After being stirred at -78°C for 1 h, the reaction mixture was allowed to warm up to -10°C and stirred for 16 h. Addition of water (15 mL) and diethyl ether (10 mL) to the mixture was followed by stirring for 30 min. The organic phase was separated and the aquous layer was extracted with ether (3x30 mL). The combined organic phases were washed with water and brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a crude oil which

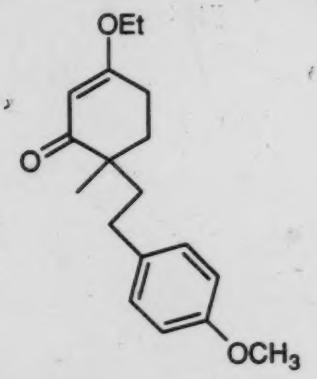
was purified by flash chromatography on silica gel, eluting with a solution of ethyl acetate and hexane (20:80) to afford alkylation product.

3-Ethoxy-6-(*p*-methoxyphenylethyl)-2-cyclohexenone (21)



Alkylation of enone **19** (830 mg, 5.95 mmol) with LDA (8.93 mmol) and 2-(*p*-methoxyphenyl)ethyl iodide **20** (5.15 g, 23.8 mmol) in THF at -10°C for 16 h gave compound **21** (864 mg, 94% yield based on consumed starting material, 44% recovery): ir ($CHCl_3$ cast) 2981, 1651 (C=O, enone), 1607 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.12 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.82 (2H, d, J = 9 Hz, 2 x Ar**H**), 5.33 (1H, s, C=C**H**CO), 3.88 (2H, q, J = 7 Hz, CH_3CH_2O), 3.78 (3H, s, OCH_3), 2.74-2.53 (2H, complex), 2.45-2.38 (2H, complex), 2.26-2.03 (3H, complex), 1.84-1.53 (2H, complex), 1.35 (3H, t, J = 7 Hz, CH_3CH_2O); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 201.5 (p), 176.9 (p), 157.8 (p), 134.1 (p), 129.3 (a), 113.8 (a), 102.3 (a), 64.2 (p), 55.3 (a), 44.5 (a), 32.3 (p), 31.6 (p), 28.0 (p), 26.4 (p), 14.2 (a); hrms M^+: 274.1565 (calcd. for $C_{17}H_{22}O_3$: 274.1569). Anal. calcd. for $C_{17}H_{22}O_3$: C 74.42, H 8.08; found: C 74.04, H 7.90.

3-Ethoxy-6-(*p*-methoxyphenylethyl)-6-methyl-2-cyclohexenone (22)



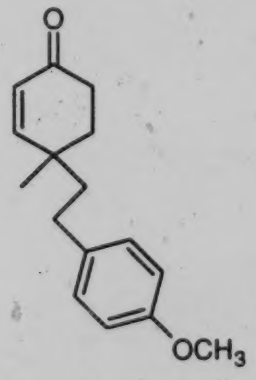
Methylation of enone **21** (719 mg, 2.62 mmol) with LDA (3.93 mmol) and iodomethane (0.49 mL, 7.89 mmol) in THF (20 mL) at room temperature for 16 h afforded compound **22** (706 mg, 94%): ir (CH_2Cl_2 cast) 2933, 1651 (C=O, enone), 1609 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.08 (2H, d, J = 9 Hz, 2 x ArH), 6.80 (2H, d, J = 9 Hz, 2 x ArH), 5.27 (1H, s, C=CHCO), 3.88 (2H, q, J = 7 Hz, CH_3CH_2O), 3.78 (3H, s, CH_3O), 2.49 (4H, complex), 2.00 (1H, complex), 1.77 (3H, complex), 1.35 (3H, t, J = 7 Hz, CH_3CH_2O), 1.14 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 203.8 (p), 175.6 (p), 157.8 (p), 134.7 (p), 129.2 (a), 113.8 (a), 101.5 (a), 64.2 (p), 55.3 (a), 43.4 (p), 39.4 (p), 32.4 (p), 29.7 (p), 26.1 (p), 22.4 (a), 14.2 (a); hrms M^+: 288.1725 (calcd. for $C_{18}H_{24}O_3$: 288.1726). Anal. calcd. for $C_{18}H_{24}O_3$: C 74.97, H 8.38; found: C 74.85, H 8.47.

General Procedure for $LiAlH_4$ Reduction Followed by Acidic Hydrolysis

A solution of alkylated enone (628 mg, 2.18 mmol) in dry diethyl ether (2 mL) was added dropwise to a stirred syspension of lithium aluminum hydride (80

mg, 2.18 mmol) in diethyl ether (10 mL) maintained at 0°C. The resulting mixture was stirred at 0°C for 30 min. Water (20 mL) was then added dropwise to destroy excess lithium aluminum hydride. At this point, a white precipitate was formed and then dissolved upon addition of 10% HCl. The mixture was acidified and stirred for 3 h at room temperature. The organic layer was separated and the aqueous fraction was repeatedly extracted with diethyl ether (3 x 15 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a solution of ethyl acetate and hexane (5:95) to give the title enone.

4-[2-(*p*-Methoxyphenyl)ethyl]-4-methyl-2-cyclohexenone (23)



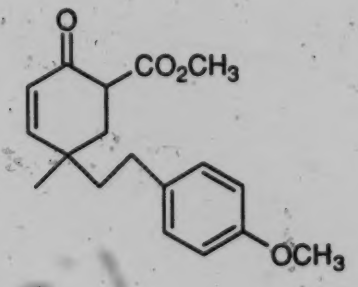
Compound **22** (628 mg, 2.18 mmol) was subjected to reduction using $LiAlH_4$ (80 mg, 2.18 mmol). This was followed by acidic hydrolysis to provide enone **23** (460 mg, 86%): ir (CH_2Cl_2 cast) 2954, 1681 (C=O, enone), 1652 (C=C), 1611 cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.09 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.84 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.72 (1H, d, J = 10 Hz, C**H**=CHCO), 5.91 (1H, d, J = 10 Hz, CH=C**H**CO), 3.82 (3H, s, OCH_3) 2.63-2.45 (4H, complex), 2.04 (1H,

complex), 1.89-1.64 (3H, complex), 1.21 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.5 (p), 158.8 (a), 157.9 (p), 134.1 (p), 129.1 (a), 127.6 (a), 114.0 (a), 55.3 (a), 43.3 (p), 35.8 (p), 34.2 (p), 33.6 (p) 29.8 (p), 24.9 (a); hrms M^+: 244.1455 (calcd. for $C_{16}H_{20}O_2$: 244.1463).

General Procedure for Carbomethoxylation

To a stirred suspension of sodium hydride (44 mg, 1.83 mmol) in dry dimethyl carbonate (10 mL) at room temperature under an argon atmosphere, was added a solution of enone (159 mg, 0.61 mmol) in dimethyl carbonate (2 mL). The reaction mixture was refluxed for 1.5 h and cooled to 0°C. A 10% HCl solution (10 mL) was cautiously added to the mixture. The resulting aqueous solution was extracted with diethyl ether (3x30 mL), and the combined organic extracts were washed with water and brine, dried over magnesium sulfate and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford the keto ester.

6-Carbomethoxy-4-(*p*-methoxyphenylethyl)-4-methyl-2-cyclohexenone (24)



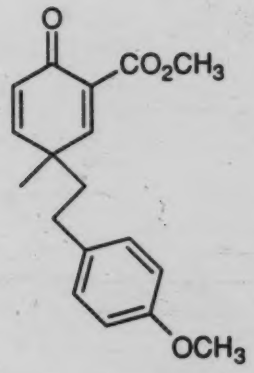
Carbomethoxylation of **23** (159 mg, 0.61 mmol) with sodium hydride (44 mg, 1.83 mmol) and dimethyl carbonate (10 mL) for 45 min gave keto ester **24** (167 mg, 91%): ir (CH_2Cl_2 cast) 2995, 1743 (C=O, ester), 1680 (C=O, ketone), 1611 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of three isomers (two epimers and an enol) in a ratio of 2:5:3, δ: 11.95 (0.2H, s, OH), 7.09 (2H, d, J = 9 Hz, 2 x ArH), 6.83 (2H, d, J = 9 Hz, 2 x ArH), 6.75 (0.3H, dd, J = 2, 10 Hz, CH=CHCO), 6.71 (0.5H, dd, J = 2, 10 Hz, CH=CHCO), 6.10 (0.2H, d, J = 10 Hz, CH=CHCO, enol), 5.95 (0.8H, d, J = 10 Hz, CH=CHCO), 5.91 (0.2H, d, J = 10 Hz, CH=CHCO, enol), 3.79 (6H, s, OCH_3), 3.62 (0.5H, dd, J = 5, 14 Hz, $COCHCO_2CH_3$), 3.57 (0.3H, dd, J = 5, 14 Hz, $COCHCO_2CH_3$), 2.72-2.42 (3H, complex), 2.38-1.94 (1H, complex), 1.91-1.53 (2H, complex), 1.25 (2.4H, s, CH_3), 1.10 (0.6H, s, CH_3, enol); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 193.8 (p), 193.7 (p), 170.9 (p), 170.8 (p), 165.2 (p), 158.9 (a), 158.6 (a), 158.1 (p), 158,0 (p), 148.3 (a), 134.6 (p), 133.7 (p), 133.6 (p), 129.2 (a),129.1 (a), 126.8 (a), 126.5 (a), 121.9 (a), 114.0 (a), 113.9 (a), 93.0 (p), 55.3 (a), 52.3 (a), 51.4 (a), 50.6 (a), 50.3 (a), 44.9 (p), 43.2 (p), 41.2 (p), 36.9 (p), 36.2 (p), 36.1 (p), 35.9 (p), 35.5 (p), 32.2 (p), 30.0 (p), 29.4 (p), 26.8 (a), 25.7 (a) 23.9 (a); hrms M^+: 302.1520 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

General Procedure for DDQ Oxidation

To a solution of keto ester (21 mg, 0.07 mmol) in dry benzene (5 mL) at room temperature under an argon atmosphere, was added DDQ (31 mg, 0.14 mmol). The mixture was stirred for 2 h at room temperature. The precipitate was removed by filtration. The filtrate was concentrated, and the residue was

subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give the enone ester.

2-Carbomethoxy-4-(*p*-methoxyphenylethyl)-4-methyl-2,5-cyclohexadienone (18)



Compound **18** was prepared by DDQ oxdation using the procedure described above. Treatment of **24** (21 mg, 0.07 mmol) with DDQ (31 mg, 0.14 mmol) in benzene (5 mL) for 2 h yielded enone ester **18** (18 mg, 85%): ir (CH_2Cl_2 cast) 2952, 1753 (C=O, ester), 1664 (C=O, ketone), 1603 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.51 (1H, d, J = 3 Hz, C**H**=CCO$_2$CH$_3$), 7.00 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.80 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.78 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 6.35 (1H, d, J = 10 Hz, CH=C**H**CO), 3.86 (3H, s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 2.40 (2H, ddd, J = 7, 7, 9.5 Hz, ArC**H**$_2$), 2.00 (2H, complex), 1.35 (3H, s, C**H**$_3$); hrms M^+: 300.1366 (calcd. for $C_{18}H_{20}O_4$: 300.1372).

General Procedure for Polyene Cyclization

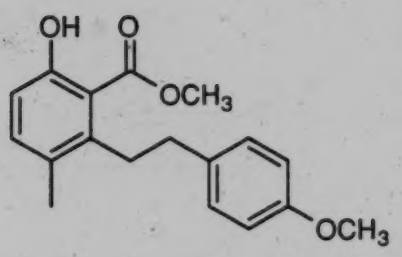
A. Using $SnCl_4$ as Lewis acid

A solution of enone ester (9 mg, 0.03 mmol) in dry dichlomethane (3 mL) was cooled to -78°C under an argon atmosphere. Stannic chloride (0.005 mL, 0.05 mmol) was added, and the mixture was stirred under the same conditions or at a higher temperature. After 16 h, the starting material was completely consumed. Water was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3x5 mL). The combined organic solutions were washed with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give the cyclization products.

B. Using $AlCl_3$ as Lewis acid

To a stirred suspension of anhydrous aluminum chloride (10 mg, 0.08 mmol) in dry diethyl ether (5 mL) at room temperature under argon, was added a solution of enone ester (15 mg, 0.05 mmol) in diethyl ether (2 mL). The reaction flask was protected from light. The reaction mixture was stirred for 1 h and then quenched with 10% HCl solution. The aqueous solution was extracted with diethyl ether (3x10 mL). The organic solution was washed with water and brine, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford the cyclization products.

Methyl 2-hydroxy-6-(*p*-methoxyphenylethyl)-5-methylbenzoate (25) and methyl 2-hydroxy-5-(*p*-methoxyphenylethyl)-6-methylbenzoate (26)



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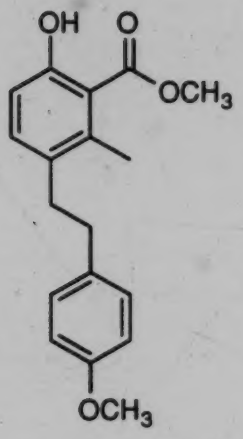


26

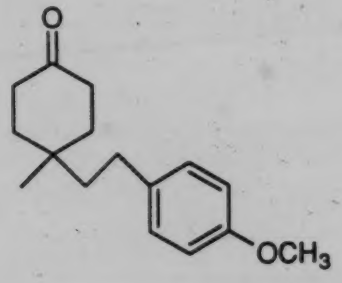
A solution of enone **18** (9 mg, 0.03 mmol) in dry dichlomethane (3 mL) was cooled to -78°C under an argon atmosphere. Stannic chloride (0.005 mL, 0.05 mmol) was added, and the mixture was warmed up to room temperature. After 16 h, the starting material was completely consumed. Water was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3x5 mL). The combined organic solutions were washed with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give an inseperable mixture of **25** and **26** (5 mg, 56%), of which the ratio was determined by ^{1}H nmr spectroscopy to be 19:1, respectively. ^{1}H nmr ($CDCl_3$, 300 MHz) since the ratio of the two isomers is so great and most of their signals are overlapped, only spectral data for the major isomer are given, δ: 10.63 (1H, s, OH), 7.24 (1H, d J = 8.5 Hz, ArH), 7.14 (2H, d, J = 9 Hz, 2 x ArH), 6.87 (2H, d, J = 9 Hz, 2 x ArH), 6.81 (1H, d, J = 8.5 Hz, ArH), 4.00 (3H, s, OCH_3), 3.81 (3H, s,

OCH_3), 3.15 (2H, complex), 2.76 (2H, complex), 2.31 (3H, s, CH_3). ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 171.8 (p), 160.3 (p), 142.1 (p), 136.8 (a), 134.3 (p), 129.1 (a), 128.1 (p), 115.5 (a), 114.0 (a), 113.0 (p), 91.9 (p), 55.4 (a), 52.3 (a), 35.5 (p), 34.2 (p), 19.7 (a); hrms M^+: 300.1366 (calcd. for $C_{18}H_{20}O_4$: 300.1362).

General Procedure for Catalytic Hydrogenation

A solution of enone (235 mg, 1.0 mmol) and 5% Pd/C (47 mg, 20% by weight) in ethyl acetate (25 mL) was shaken under hydrogen (2 atm) for 3 h, then filtered through celite and evaporated. The crude product obtained was then purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give the ketone.

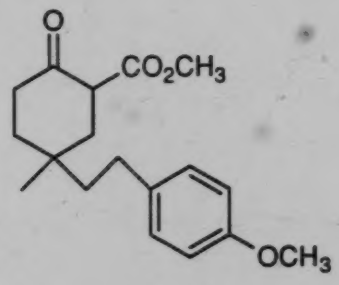
4-(*p*-Methoxyphenylethyl)-4-methylcyclohexanone (27)



Enone **23** (235 mg, 1.0 mmol) was subjected to catalytic hydrogenation with 5% Pd/C for 3 h under hydrogen (2 atm) using ethyl acetate as the solvent to give ketone **27** (210 mg, 91%): ir (CH_2Cl_2 cast) 2932, 1714 (C=O), 1611 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.10 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.85 (2H, d, J = 9

Hz, 2 x ArH), 3.78 (3H, s, OCH_3), 2.55 (2H, complex), 2.37 (4H, complex), 1.82-1.62 (6H, complex), 1.15 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 212.4 (p), 157.8 (p), 134.8 (p), 129.1 (a), 113.9 (a), 55.3 (a), 43.1 (p), 37.6 (p), 37.3 (p), 32.4 (p), 29.5 (p), 23.0 (a); hrms M^+: 246.1616 (calcd. for $C_{16}H_{22}O_2$: 246.1620). Anal. calcd. for $C_{16}H_{22}O_2$: C 78.01, H 9.00; found: C 77.80, H 9.09.

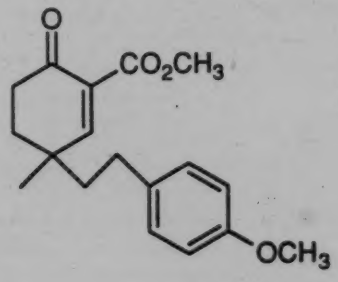
2-Carbomethoxy-4-[2-(*p*-methoxyphenyl)ethyl]-4-methylcyclohexanone (28)



Compound **28** was prepared according to the general procedure for carbomethoxylation. Treatment of **27** (187 mg, 0.8 mmol) with sodium hydride (60 mg, 2.4 mmol) in refluxing dimethyl carbonate (10 mL) for 45 min gave keto ester **28** (206 mg, 90%): ir (CH_2Cl_2 cast) 2931, 1745 (C=O, ester), 1716 (C=O, ketone), 1656 (C=O, enol ester) and 1614 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture existed mostly in the enol form (80%) δ: 12.17 (1H, s, OH), 7.10 (2H, d, J = 9 Hz, 2 x ArH), 6.83 (2H, d, J = 9 Hz, 2 x ArH), 3.82 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.56 (1H, d, J = 8.5 Hz, CH_2C=C-OH), 2.54 (1H, d, J = 8.5 Hz, CH_2C=C-OH), 2.31 (2H, t, J = 6.5 Hz, $ArCH_2$), 2.09 (2H, complex), 1.64-1.44 (4H, complex), 1.01 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 173.2 (p), 171.4 (p), 157.7 (p), 135.0 (p), 129.2 (a), 113.9 (a), 96.1 (p), 55.3 (a),

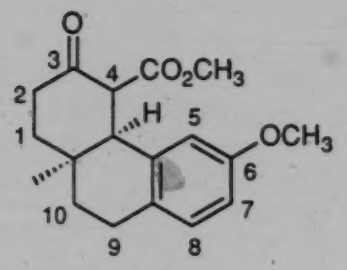
51.4 (a), 43.4 (p), 34.8 (p), 32.5 (p), 31.7 (p), 29.3 (p), 26.3 (p), 24.2 (a); hrms M^+: 304.1668 (calcd. for $C_{18}H_{24}O_4$: 304.1674). Anal. calcd. for $C_{18}H_{24}O_4$: C 71.03, H 7.95; found: C 71.09, H 8.05.

2-Carbomethoxy-4-(*p*-methoxyphenylethyl)-4-methyl-2-cyclohexenone (29)



Using the general procedure, oxidation of keto ester **28** (25 mg, 0.08 mmol) using DDQ (60 mg, 0.24 mmol) in benzene was carried out at room temperature for 1 h to give enone ester **29** (20 mg, 83 %): ir (CH_2Cl_2 cast) 2932, 1743 (C=O, ester), 1687 (C=O, ketone), 1611 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.40 (1H, s, C**H**=CCO_2CH_3), 7.09 (2H, d, J = 9 Hz, 2 x Ar**H**), 6.83 (2H, d, J = 9 Hz, 2 x Ar**H**), 3.81 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.70-2.50 (4H, complex), 2.07 (1H, complex), 1.91-1.75 (3H, complex), 1.28 (3H, s, CH_3); hrms M^+: 302.1514 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

(4aR*, 10aS*)-4-Carbomethoxy-3-hydroxy-6-methoxy-10a-methyl-1,2,4a,9,10,10a-hexahydrophenanthrene (30)



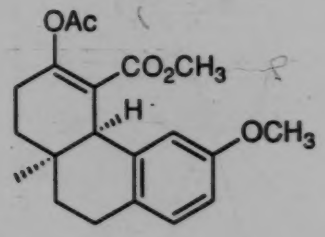
Enone ester **29** (15 mg, 0.05 mmol) was treated with stannic chloride (0.01 mL, 0.08 mmol) for 1 day at room temperature in dichloromethane (5 mL) to provide the hydrophenanthrene **30** (12 mg, 84%): ir (CH_2Cl_2 cast) 2928, 1748 (C=O, ester), 1712 (C=O, ketone), 1650 (C=O, enol ester), 1609 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture exists mostly in the enol form (87%) δ: 12.60 (1H, s, O**H**), 6.97 (1H, d, J = 9 Hz, Ar**H**), 6.62 (1H, dd, J = 1.5, 9 Hz, Ar**H**), 6.45 (1H, d, J = 1.5 Hz, Ar**H**), 3.74 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.36 (1H, br. s, ring junction **H**), 2.67 (2H, dd, J = 7, 7 Hz, $ArCH_2$), 2.45-2.15 (2H, complex), 1.95-1.79 (1H, complex), 1.53-1.13 (3H, complex), 1.08 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 173.9 (p), 173.8 (p), 157.8 (p), 141.9 (p), 129.7 (p), 128.2 (a), 114.1 (a), 110.5 (a), 99.0 (p), 55.2 (a), 51.6 (a), 42.9 (a), 38.1 (p), 32.3 (p), 28.9 (p), 26.7 (p), 26.0 (p), 25.9 (a); hrms M^+: 302.1516 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

General Procedure for Acetylation of β-Keto Ester

To a solution of keto ester (47 mg, 0.16 mmol), in pyridine (5 mL) at room temperature under an argon atmosphere, were added acetic anhydride (1 mL) and DMAP (cat.). The reaction mixture was stirred overnight, and pyridine was removed under reduced pressure. Water was added and the resulting mixture

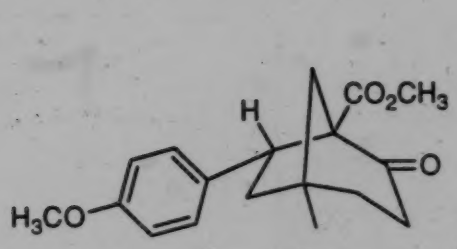
was extracted with diethyl ether (3x10 mL). The ether extracts were washed with 10% hydrochloric acid and brine, dried over magnesium sulfate, fitered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (20:80) as an eluent gave the enol acetate.

(4aR*, 10aS*)-3-Acetoxy-4-carbomethoxy-6-methoxy-10a-methyl-1,2,4a,9,10,10a-hexahydrophenanthrene (31)

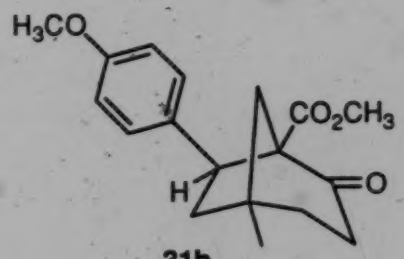


Hydrophenanthrene **30** (12 mg, 0.04 mmol) was treated with pyridine and acetic anhydride to give enol acetate **31** (6.6 mg, 54% yield) along with 42% recovery of **30**. Compound **31**: ir (CH_2Cl_2 cast) 2929, 1763 (C=O, CH_3CO_2), 1718 (C=O, CH_3OCO), 1610 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 6.99 (1H, d, J = 9 Hz, ArH), 6.68 (1H, dd, J = 2.5, 9 Hz, ArH), 6.85 (1H, d, J = 2.5 Hz, ArH), 3.73 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.62 (1H, s, ring junction H), 2.69 (2H, dd, J = 7, 7 Hz, $ArCH_2$), 2.28 (2H, complex), 2.20 (3H, s, CH_3CO_2), 1.79 (1H, complex), 1.57-1.42 (2H, complex), 1.35 (1H, complex), 1.24 (3H. s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 157.9 (p), 155.4 (p), 155.0 (p), 146.6 (p), 140.2 (p), 129.6 (p), 128.4 (a), 120.0 (p), 113.4 (a), 111.9 (a), 55.2 (a), 51.9 (a), 45.6 (a), 36.5 (p), 32.1 (p), 30.7 (p), 26.7 (p), 26.0 (p), 25.7 (a), 21.0 (a); hrms M^+: 344.1620 (calcd. for $C_{20}H_{24}O_5$: 344.1624). Anal. calcd. for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found: C 69.51, H 7.12.

(1S*, 5S*, 7S*)-1-Carbomethoxy-7-*p*-methoxyphenyl-5-methylbicyclo[3.2.1]octan-2-one (31a) and (1S*, 5S*, 7R*)-1-carbomethoxy-7-*p*-methoxyphenyl-5-methylbicyclo[3.2.1]octan-2-one (31b)



31a

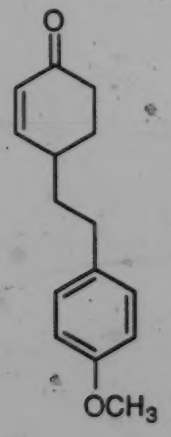


31b

Keto ester **29** (78 mg, 0.26 mmol) was stirred in chloroform in the presence of DDQ at room temperature under an argon atmosphere. After 20 min, the mixture was filtered through celite using chloroform and concentrated. The crude product was then purified by flash chromatography using ethyl acetate/hexane (20:80) to give compounds **31a** (26 mg, 33%) and **31b** (27 mg, 35 %) with 7% recovery of starting material. Compound **31a**: ir (CH_2Cl_2 cast) 2952, 1739 (C=O, ester), 1710 (C=O, ketone), 1612 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.20 (2H, d, J = 9 Hz, 2 x ArH), 6.79 (2H, d, J = 9 Hz, 2 x ArH), 4.05 (1H, dd, J = 6.5, 12 Hz, ArCH), 3.76 (6H, s, OCH_3), 2.50 (1H, dd, J = 13, 13 Hz, CH_2), 2.36 (1H, ddd, J = 5, 5, 17 Hz, CH_2), 2.20 (2H, s, C8-H), 2.10 (2H, m, CH_2), 1.73 (2H, dd, J = 5, 10 Hz, CH_2), 1.22 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 207.7 (p), 172.3 (p), 157.9 (p), 132.5 (p), 128.8 (a), 113.5 (a), 69.2 (p), 55.2 (a), 52.2 (a), 49.9 (p), 47.2 (a), 43.6 (p), 39.4 (p), 38.5 (p), 37.4 (p), 26.1 (a); hrms M^+: 302.1519 (calcd. for $C_{18}H_{22}O_4$: 302.1518). Compound **31b**: ir (CH_2Cl_2 cast) 2949, 1738 (C=O, ester, 1710 (C=O, ketone), 1613 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.10 (2H, d, J = 9 Hz, 2 x ArH), 6.80 (2H, d, J

= 9 Hz, 2 x Ar**H**), 3.78 (3H, s, OCH_3), 3.54 (1H, dd, J = 6, 9 Hz, Ar**CH**), 3.22 (3H, s, OCH_3), 2.79 (1H, ddd, J = 9, 12.5, 15.5 Hz, H_3), 2.62 (1H, dd, J = 3.5, 13 Hz, H_8), 2.47 (1H, ddd, J = 2, 9, 14 Hz, H_6), 2.40 (1H, ddd, J = 1, 6.5, 15.5, H_3), 2.00 (1H, ddd, J = 2, 6, 14 Hz, H_6), 1.88 (1H, dd, J = 1, 13 Hz, H_8), 1.75 (2H, complex), 1.30 (3H, s CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 207.5 (p), 170.4 (p), 158.4 (p), 136.1 (p), 129.2 (a), 113.6 (a), 71.5 (p), 55.3 (a), 51.3 (a), 49.9 (a), 47.9 (p), 47.1 (p), 39.9 (p), 39.4 (p), 35.8 (p), 25.7 (a); hrms M^+: 302.1519 (calcd. for $C_{18}H_{22}O_4$: 302.1518).

4-(*p*-Methoxyphenylethyl)-2-cyclohexenone (32)



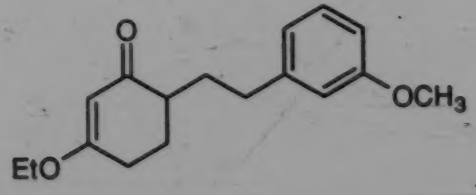
A solution of compound **21** (84 mg, 0.31 mmol) in dry diethyl ether (2 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (11 mg, 0.31 mmol) in diethyl ether (5 mL). The reaction mixture was maintained at 0°C for 10 min which was followed by hydrolysis with 10% HCl to furnish enone **32** (63 mg, 90%): ir ($CHCl_3$ cast) 2918, 1678 (C=O, ketone), 1611 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.12 (2H, ddd, J = 2, 3, 9 Hz, 2 x Ar**H**), 6.88 (1H, ddd, J = 1.5, 2.5, 10 Hz, C**H**=CHCO), 6.85 (2H, ddd, J = 2, 3, 9 Hz, 2 x Ar**H**), 5.99 (1H,

dd, J = 2.5, 10 Hz, CH=CHCO), 3.78 (3H, s, OCH_3), 2.74-2.61 (2H, complex), 2.59-2.28 (3H, complex), 2.22-2.10 (1H, complex), 1.91-1.64 (3H, complex); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.8 (p), 158.0 (p), 154.8 (a), 133.5 (p), 129.3 (a), 129.2 (a), 114.0 (a), 55.3 (a), 36.9 (p), 36.5 (p), 35.4 (a), 32.2 (p), 28.6 (p); hrms M^+: 230.1306 (calcd. for $C_{15}H_{18}O_2$: 230.1307). Anal. calcd for $C_{15}H_{18}O_2$: C 78.23, H 7.88; found: C 78.33, H 8.02.

2-(*m*-Methoxyphenyl)ethyl iodide

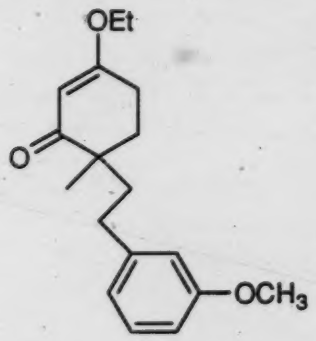
Using the above general procedure, 2-(*m*-methoxyphenyl)ethanol (1.1 g, 7.2 mmol) was treated with carbon tetraiodide (4.5 g, 8.6 mmol) and triphenylphosphine (2.8 g, 10.8 mmol) in dry dichloromethane (10 mL) to produce the corresponding iodide (1.63 g, 86%): ir (CH_2Cl_2 cast) 2999, 1600 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.22 (1H, dd, J = 8, 8 Hz, ArH), 6.76 (3H, complex, 3 x ArH), 3.80 (3H, s, OCH_3), 3.33 (2H, dt, J = 1, 7.5 Hz, CH_2I), 3.13 (2H, t, J = 7.5 Hz, $ArCH_2$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 159.8 (p), 142.2 (p), 129.7 (a), 120.7 (a), 114.2 (a), 112.2 (a), 55.2 (a), 40.5 (p), 5.3 (p); hrms M^+: 261.9846 (calcd. for $C_9H_{11}IO$: 261.9855). Anal. calcd. for $C_9H_{11}IO$: C 41.25, H 4.23; found: C 41.13, H 4.31.

3-Ethoxy-6-(*m*-methoxyphenylethyl)-2-cyclohexenone (34)



Following the general procedure previously described, alkylation of enone **19** (603 mg, 4.30 mmol) with LDA (6.45 mmol) and 2-(*m*-methoxyphenyl)ethyl iodide (2.98 g, 11.4 mmol) in THF at -20°C for 16 h gave compound **34** (610 mg, 73% yield based on consumed starting material (30% recovery)): ir (CH_2Cl_2 cast) 2938, 1653 (C=O, ketone), 1608 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.16 (1H, dd, J = 8, 8 Hz, ArH), 6.78 (1H, br. d, J = 8 Hz, ArH), 6.73 (1H, br. s, ArH), 6.70 (1H, dd, J = 2, 8 Hz, ArH), 5.29 (1H, s, C=CHCO), 3.86 (2H, q, J = 7 Hz, CH_3CH_2O), 3.78 (3H, s, OCH_3), 2.65 (2H, complex), 2.40 (2H, dd, J = 6.5, 6.5 Hz, $ArCH_2$), 2.25-2.00 (3H, complex), 1.82-1.55 (2H, complex), 1.34 (3H, t, J = 7 Hz, CH_3CH_2O); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 201.3 (p), 176.7 (p), 159.7 (p), 143.7 (p), 129.3 (a), 120.9 (a), 114.1 (a), 111.2 (a), 102.2 (a), 64.2 (p), 55.1 (a), 44.5 (a), 33.3 (p), 31.3 (p), 28.0 (p), 26.4 (p), 14.1 (a); hrms M^+: 274.1566 (calcd. for $C_{17}H_{22}O_3$: 274.1569). Anal. calcd. for $C_{17}H_{22}O_3$: C 74.42, H 8.08; found: C 74.03, H 8.21.

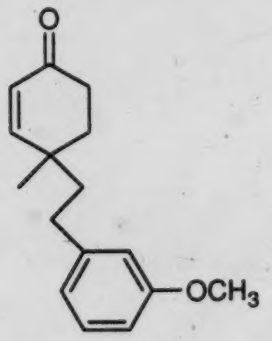
3-Ethoxy-6-(*m*-methoxyphenylethyl)-6-methyl-2-cyclohexenone (35)



Following the standard procedure, methylation of enone **34** (575 mg, 2.09 mmol) with LDA (3.16 mmol) and iodomethane (0.39 mL, 6.27 mmol) in THF (20

mL) at room temperature for 16 h afforded compound **35** (581 mg, 97%): ir (CH_2Cl_2 cast) 2936, 1650 (C=O, ketone), 1609 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.18 (1H, dd, J = 8, 8 Hz, Ar**H**), 6.75 (3H, complex, 3 x Ar**H**), 5.28 (1H, s, C=C**H**CO), 3.89 (2H, q, J = 7 Hz, CH_3CH_2O), 3.79 (3H, s, OCH_3), 2.53 (2H, ddd, J = 3.5, 6, 10.5 Hz, CH_2), 2.46 (1H, dd, J = 4, 6 Hz, CH_2), 2.44 (1H, dd, J = 3, 6 Hz, CH_2), 2.00 (1H, complex), 1.92-1.68 (3H, complex), 1.36 (3H, t, J = 7 Hz, CH_3CH_2O), 1.17 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 203.7 (p), 175.7 (p), 159.7 (p), 144.3 (p), 129.3 (a), 120.8 (a), 114.1 (a), 111.1 (a), 101.4 (a), 64.2 (p), 55.2 (a), 43.4 (p), 39.0 (p), 32.4 (p), 30.7 (p), 26.1 (p), 22.4 (a), 14.2 (a); hrms M^+: 288.1717 (calcd. for $C_{18}H_{24}O_3$: 288.1726). Anal. calcd. for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 74.76, H 8.34.

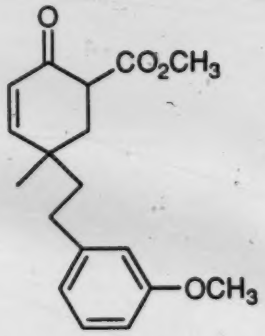
4-(*m*-Methoxyphenylethyl)-4-methyl-2-cyclohexenone (36)



Compound **36** was prepared according to the general procedure for $LiAlH_4$ reduction followed by acid hydrolysis. Compound **35** (473 mg, 1.64 mmol) was subjected to reduction with $LiAlH_4$ (62 mg, 1.64 mmol), followed by acid hydrolysis to produce enone **36** (350 mg, 88%): ir (CH_2Cl_2 cast) 2934, 1680 (C=O, ketone), 1601 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.21 (1H, dd, J =

8, 8 Hz, ArH), 6.75 (4H, complex, 3 x ArH and CH=CHCO), 5.92 (1H, d, J = 10 Hz, CH=CHCO), 3.81 (3H, s, OCH_3), 2.61 (2H, ddd, J = 7, 7, 9 Hz, $ArCH_2$), 2.50 (1H, dd, J = 2.5, 6, H_6), 2.48 (1H, d, J = 6 Hz, H_6), 2.04 (1H, complex), 1.90-1.68 (3H, complex), 1.23 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.4 (p), 159.8 (p), 158.7 (a), 143.7 (p), 129.5 (a), 127.7 (a), 120.6 (a), 114.2 (a), 111.2 (a), 55.2 (a), 42.9 (p), 35.8 (p), 34.1 (p), 33.5 (p), 30.8 (p), 24.9 (a); hrms M^+: 244.1459 (calcd. for $C_{16}H_{20}O_2$: 244.1463). Anal. calcd. for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.26, H 8.41.

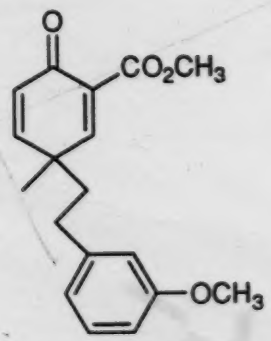
6-Carbomethoxy-4-(*m*-methoxyphenylethyl)-4-methyl-2-cyclohexenone (37)



Enone **36** (299 mg, 1.22 mmol) was subjected to previously described standard carbomethoxylation using sodium hydride (90 mg, 3.66 mmol) and dimethyl carbonate (10 mL). After refluxing for 1 h, the crude product was purified on silica gel to give keto ester **37** (352 mg, 95%): ir (CH_2Cl_2 cast) 2952, 1743 (C=O, ester), 1680 (C=O, ketone), 1601 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of two keto epimers and an enol tautomer in a ratio of 5:3.5:1.5, repectively, δ: 11.88 (0.15H, s, OH), 7.23 (0.35H, d, J = 8 Hz, ArH, keto), 7.18

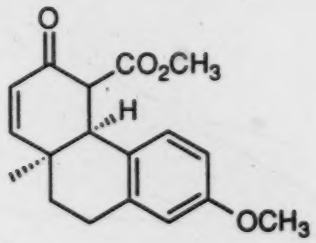
(0.5H, d, J = 8 Hz, ArH, keto), 7.14 (0.15H, d, J = 8 H, ArH, enol), 6.72 (3.85H, complex, 3 x ArH and 0.85 x CH=CHCO, keto), 6.08 (0.15H, d, J = 10 Hz, CH=CHCO, enol), 5.94 (0.85, d, J = 10 Hz, CH=CHCO, keto), 5.90 (0.15H, J = 10 Hz, CH=CHCO, enol), 3.78 (5.1H, s, OCH_3, keto), 3.77 (0.45H, s, OCH_3, enol), 3.75 (0.45H, s, OCH_3, enol), 3.60 (0.5H, dd, J = 5, 14 Hz, $CHCO_2CH_3$, keto), 3.55 (0.35H, dd, J = 5, 13 Hz, $CHCO_2CH_3$, keto), 2.74-2.40 (2.5H, complex), 2.36-2.08 (1H, complex), 2.01-1.55 (2.5H, complex), 1.23 (2.55H, s, CH_3, ketone), 1.09 (0.45H, s, CH_3, enol); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 193.8 (p), 193.7 (p), 170.9 (p), 170.8 (p), 165.2 (p), 159.8 (p), 159.7 (p), 158.7 (a), 158.5 (a), 148.2 (a), 144.2 (p), 143.3 (p), 143.2 (p), 129.6 (a), 129.6 (a), 129.4 (a), 126.9 (a), 126.6 (a), 122.0 (a), 120.7 (a), 120.7 (a), 120.6 (a), 114.2 (a), 114.1 (a), 111.4 (a), 111.4 (a), 111.1 (a), 93.0 (p), 55.2 (a), 52.3 (a), 51.5 (a), 50.6 (a), 50.3 (a), 44.6 (p), 42.8 (p), 40.9 (p), 36.9 (p), 36.2 (p), 36.1 (p), 35.9 (p), 35.6 (p), 32.2 (p), 31.1 (p), 31.0 (p), 30.5 (p), 26.8 (a), 25.7 (a), 24.0 (a); hrms M^+: 302.1513 (calcd. for $C_{18}H_{22}O_4$: 302.1518). Anal. calcd. for $C_{18}H_{22}O_4$: C 71.50, H 7.33; found: C 71.34, H 7.30.

2-Carbomethoxy-4-(*m*-methoxyphenylethyl)-4-methyl-2,5-cyclohexadienone (33)



According to the procedure described above for the DDQ oxidation, to a solution of compound **37** (63 mg, 0.21 mmol) in dichloromethane (5 mL) was added DDQ (142 mg, 0.80 mmol) at room temperature, and the reaction mixture was stirred for 4 h. After usual work up, the crude product was purified to afford enone ester **33** (61 mg, 98%): ir (CH_2Cl_2 cast) 2950, 1742 (C=O, ester), 1666 (C=O, ketone), 1601 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.56 (1H, d, J = 3 Hz, C**H**=CCO$_2$CH$_3$), 7.17 (1H, dd, J = 8, 8 Hz, Ar**H**), 6.79 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 6.72 (1H, dd, J = 2.5, 8 Hz, Ar**H**), 6.68 (1H, br. d, J = 8 Hz, Ar**H**), 6.63 (1H, br. s, Ar**H**), 6.35 (1H, d, J = 10 Hz, CH=C**H**CO), 3.86 (3H. s, OC**H**$_3$), 3.78 (3H, s, OC**H**$_3$), 2.40 (2H, ddd, J = 7, 7, 9.5 Hz, ArC**H**$_2$), 2.02 (2H, complex), 1.35 (3H, s, C**H**$_3$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 181.5 (p), 165.1 (p), 160.5 (a), 159.8 (p), 153.4 (a), 142.4 (p), 131.7 (p), 129.9 (a), 129.5 (a), 120.5 (a), 114.0 (a), 111.6 (a), 55.2 (a), 52.3 (a), 42.3 (p), 42.1 (p), 31.6 (p), 26.0 (a); hrms M$^+$: 300.1355 (calcd. for $C_{18}H_{20}O_4$: 300.1362). Anal. calcd. for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.93, H 6.62.

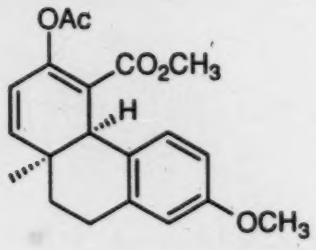
(4aS*, 10aR*)-4-Carbomethoxy-7-methoxy-10a-methyl-3-oxo-3,4, 4a,9,10,10a-hexahydrophenanthrene (38)



Enone ester **33** (47 mg, 0.16 mmol) was treated with stannic chloride (0.03 mL, 0.23 mmol) in dichloromethane (5 mL) at -78°C for 30 min to provide compound

38 (47 mg, 100%): ir (CH_2Cl_2 cast) 2950, 1743 (C=O, ester), 1678 (C=O, ketone), 1654 (C=O, enol), 1621 (C=C, enol) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of three isomers in a ratio of 3:3:4, δ: 12.14 (0.4H, s, O**H**), 6.97 (0.6H, d, J = 8 Hz, Ar**H**, keto), 6.92 (0.4H, d, J = 8 Hz, Ar**H**, enol), 6.85 (0.6H, d, J = 10 Hz, C**H**=CHCO, keto), 6.67 (1.6H, complex, Ar**H**), 6.55 (0.4H, d, J = 2.5 Hz, Ar**H**, enol), 6.14 (0.4H, dd, J = 1.5, 10 Hz, CH=C**H**CO, enol), 6.02 (0.6H, d, J = 10 Hz, CH=C**H**CO, keto), 5.85 (0.4H, d, J = 10 Hz, C**H**=CHCO, enol), 3.88 (1.2H, s, OCH_3, enol), 3.76 (1.8, s, OCH_3, keto), 3.74 (1.2H, s, OCH_3, enol), 3.69 (1.8H, s, OCH_3, keto), 3.61 (0.4H, s, ring junction **H**, enol), 3.44 (0.6H, s, $CHCO_2CH_3$, keto), 3.43 (0.6H, s, ring junction **H**, keto), 3.00-2.70 (2H, complex), 1.95-1.65 (2H, complex), 1.14 (1.2H, s, CH_3, enol), 1.11 (1.8H, s, CH_3, keto); hrms M^+: 300.1357 (calcd. for $C_{18}H_{20}O_4$: 300.1362).

(4aR*, 10aR*)-3-Acetoxy-4-carbomethoxy-7-methoxy-10a-methyl-4a,9,10,10a-tetrahydrophenathrene (39)



Following the previously described procedure for acetylation, a mixture of **38** (47 mg, 0.16 mmol) was treated with pyridine and acetic anhydride for 16 h at room temperature to give acetate **39** (42 mg, 80%): ir (CH_2Cl_2 cast) 2952, 1765 (C=O, ester), 1707 (C=O, ketone), 1610 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 6.96 (1H, d, J = 8 Hz, Ar**H**), 6.68 (1H, dd, J = 2.5, 8 Hz, Ar**H**), 6.57 (1H,

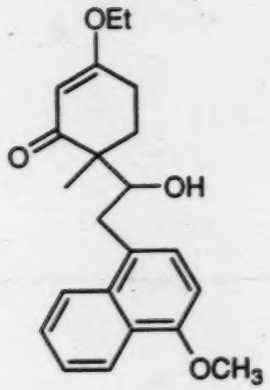
d, J = 2.5 Hz, ArH), 6.08 (1H, dd, J = 1.5, 10 Hz, CH=CHCOAc), 5.66 (1H, d, J = 10 Hz, CH=CHCOAc), 3.82 (3H, s, OCH_3), 3.79 (1H, br. s, ring junction H), 3.72 (3H, s, OCH_3), 2.93-2.68 (2H, complex), 2.24 (3H, s, O_2CCH_3), 1.98-1.78 (2H, complex), 1.23 (3H, s, CH_3); ^{13}C APT ($CDCl_3$, 75 MHz) δ: 168.4 (p), 167.0 (p), 157.8 (p), 152.0 (p), 146.4 (a), 137.3 (p), 129.3 (p), 128.9 (a), 123.8 (a), 116.1 (p), 113.0 (a), 112.2 (a), 55.1 (a), 52.1 (a), 43.0 (a), 36.4 (p), 34.3 (p), 27.9 (p), 24.7 (a), 21.0 (a); hrms M^+: 342.1462 (calcd. for $C_{20}H_{22}O_5$: 342.1467). Anal. calcd. for $C_{20}H_{22}O_5$: C 70.16, H 6.48; found: C 69.93, H 6.66.

4-Methoxy-1-naphthaleneacetaldehyde

To a stirred suspension of methoxymethyltriphenylphosphonium chloride (6.63 g, 19.4 mmol) in THF (50 mL) at 0°C under an atmosphere of argon was added dropwise *n*-butyllithium (2.5 M in hexane, 9.67 mL, 15.5 mmol). The reaction mixture was stirred at 0°C for 1 h and was then warmed up to room temperature. After stirring at room temperature for 2 h (solution turned homogeneous with a blood-red color), a solution of 4-methoxy-1-naphthaldehyde (2.4 g, 12.9 mmol) in THF (5 mL) was added slowly. The reaction mixture was stirred at room temperature for 16 h, and then water was added to quench the reaction. The aqueous solution was extracted with ether (3x50 mL) and the combined organic extracts were washed with water and brine. It was then dried over magnesium sulfate, filtered and concentrated. The crude product was then dissolved in THF and 10% HCl (1:1, 50 mL) at room temperature. The resulting solution was stirred for 2 days and then water (20 mL) was added. The aqueous solution was extracted with diethyl ether (3x50 mL). The extracts were washed with water and brine, dried (MgSO4), filtered and concentrated. Flash

chromatography of the residue using ethyl acetate/hexane (20:80) afforded the 4-methoxynaphthaleneacetaldehyde (1.62 g, 63%): ir (CH_2Cl_2 cast) 3073, 1723 (C=O, aldehyde), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 9.75 (1H, t, J = 2.5 Hz, CHO), 8.34 (1H, dd, J = 1.5, 8 Hz, ArH), 7.80 (1H, dd, J = 1.5, 8 Hz, ArH), 7.54 (2H, complex, 2 x ArH), 7.31 (1H, d, J = 8 Hz, ArH), 6.80 (1H, d, J = 8 Hz, ArH), 4.02 (3H, s, OCH_3), 4.01 (2H, d, J = 2.5 Hz, CH_2); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 200.1 (a), 155.6 (p), 133.1 (p), 128.5 (a), 127.2 (a), 126.1 (p), 125.4 (a), 123.7 (a), 122.9 (a), 120.2 (p), 103.5 (a), 55.6 (a), 47.9 (p); hrms M^+: 200.0835 (calcd. for $C_{13}H_{12}O_2$: 200.0837.

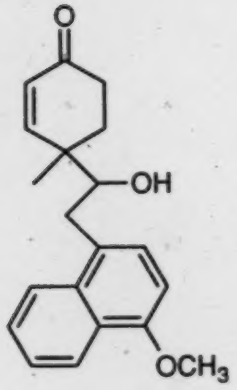
3-Ethoxy-6-[1-hydroxy-2-(4-methoxy-1-naphthyl)ethyl]-6-methyl-2-cyclohexenone (42)



To a solution of diisopropylamine (0.08 mL, 0.64 mmol) in THF (5 mL) was added *n*-butyllithium (2.5 M in hexane, 0.23 mL, 0.56 mmol) at -78°C, and the mixture was stirred for 15 min. To the resulting mixture was added enone **41** (78 mg, 0.38 mmol) in THF (2 mL) dropwise, and the mixtrue was stirred for 30 min. 4-Methoxy-1-naphthaleneacetaldehyde (160 mg, 0.80 mmol) in THF (2

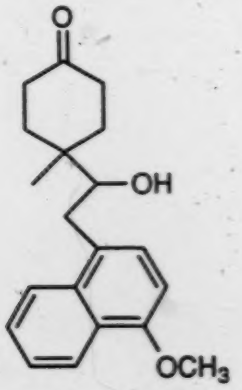
mL) was added to the mixture and again stirred for 30 min. The reaction mixture was quenched with saturated NH_4Cl (5 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography through silica gel with 20% ethyl acetate-hexane to give the alcohols **42** (0.158 mg, 88%): ir (CH_2Cl_2 cast) 3418 (OH), 3073 (Ar-H), 1635 (C=O, ketone), 1604 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 8.32 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 8.14 (1H, d, J = 8 Hz, Ar**H**), 7.58 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.49 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.31 (1H, d, J = 8 Hz, Ar**H**), 6.76 (1H, d, J = 8 Hz, Ar**H**), 5.31 (1H, d, J = 1 Hz, C=C**H**CO), 4.19 (1H, dd, J = 2, 10 Hz, C**H**OH), 3.98 (3H, s, OC**H**$_3$), 3.92 (2H, q, J = 7 Hz, CH_3CH_2O), 3.43 (1H, br. s, O**H**), 3.27 (1H, dd, J = 2, 14 Hz, ArC**H**$_2$), 2.84 (1H, dd, J = 10, 14 Hz, ArC**H**$_2$), 2.59 (1H, dd, J = 5.5, 11 Hz, **H**$_4$), 2.41 (1H, dd, J = 3.5, 5.5 Hz, **H**$_4$), 2.08 (1H, dd, J = 5.5, 11 Hz, **H**$_5$), 2.02 (1H, dd, J = 3.5, 5.5 Hz, **H**$_5$), 1.39 (3H, t, J = 7 Hz, CH_3CH_2O), 1.32 (3H, s, C**H**$_3$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) for the major diastereoisomer, δ: 205.6 (p), 176.8 (p), 154.6 (p), 133.0 (p), 127.6 (a), 127.1 (p), 126.4 (a), 126.1 (p), 124.9 (a), 124.0 (a), 122.6 (a), 103.4 (a), 101.6 (a), 75.5 (a), 64.4 (p), 55.5 (a), 47.0 (p), 34.5 (p), 28.7 (p), 25.9 (p), 17.7 (a), 14.1 (a); for the minor diastereoisomer, δ: 205.6 (p), 176.8 (p), 154.6 (p), 132.9 (p), 127.5 (a), 127.1 (p), 126.4 (a), 126.1 (p), 124.9 (a), 123.6 (a), 122.7 (a), 103.4 (a), 102.0 (a), 74.8 (a), 64.4 (p), 55.5 (a), 48.3 (p), 34.1 (p), 27.8 (p), 25.9 (p), 19.1 (a), 14.1 (a); hrms M^+: 354.1831 (calcd. for $C_{22}H_{26}O_4$: 354.1831).

4-[1-Hydroxy-2-(4-methoxy-1-naphthyl)ethyl]-4-methyl-2-cyclohexenone (43)



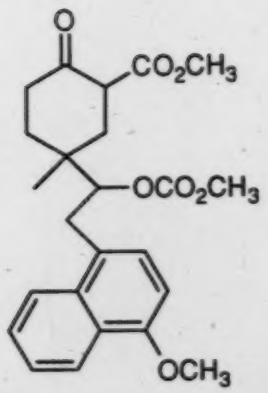
Compounds **43** were prepared according to the general procedure for $LiAlH_4$ reduction followed by acid hydrolysis. Compounds **42** (100 mg, 0.28 mmol) were subjected to reduction with $LiAlH_4$ (20 mg, 0.28 mmol) in THF (5 mL) at 0°C for 10 min to afford **43** (71 mg, 82%): ir (CH_2Cl_2 cast) 3426 (OH), 1672 (C=O, ketone), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 8.33 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 7.88 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 7.57 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.52 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.28 (1H, d, J = 8 Hz, Ar**H**), 7.04 (1H, dd, J = 1.5, 10 Hz, C**H**=CHCO), 6.77 (1H, d, J = 8 Hz, Ar**H**), 6.01 (1H, d, J = 10 Hz, CH=C**H**CO), 3.99 (3H, s, OCH_3), 3.79 (1H, dd, J = 2, 11 Hz, C**H**OH), 3.43 (1H, dd, J = 2, 14 Hz, ArCH_2), 2.87 (1H, dd, J = 11, 14 Hz, ArCH_2), 2.59 (2H, complex), 2.30 (1H, dd, J = 8.5, 13.5 Hz, CH_2), 2.00 (1H, complex), 1.61 (1H, br. s, O**H**), 1.34 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.4 (p), 156.1 (a), 155.1 (p), 132.8 (p), 128.3 (a), 127.9 (a), 126.9 (a), 126.4 (p), 125.7 (p), 125.3 (a), 123.2 (a), 123.0 (a), 103.4 (a), 76.3 (a), 55.6 (a), 40.4 (p), 35.0 (p), 34.2 (p), 30.8 (p), 20.1 (a); hrms M^+: 310.1585 (calcd. for $C_{20}H_{22}O_3$: 310.1569).

4-[1-Hydroxy-2-(4-methoxy-1-naphthyl)ethyl]-4-methylcyclohexanone (44)



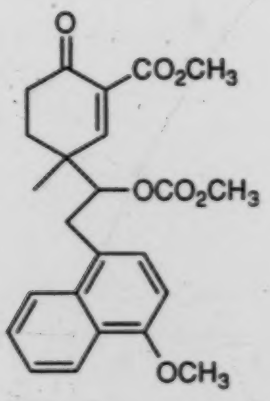
Following the general procedure for catalytic hydrogenation, enones **43** (196 mg, 0.63 mmol) were hydrogenated using Wilkinson's catalyst (292 mg, 0.32 mmol) in benzene at room temperature under H_2 atmosphere (2 atm) for 6 h to furnish saturated ketones **44** (204 mg, 100%): ir (CH_2Cl_2 cast) 3453 (OH), 3005 (Ar-H), 1711 (C=O, ketone), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 8.33 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 7.89 (1H, br. d, J = 8 Hz, Ar**H**), 7.55 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.49 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.25 (1H, d, J = 8 Hz, Ar**H**), 6.74 (1H, d, J = 8 Hz, Ar**H**), 3.96 (3H, s, OCH_3), 3.63 (1H, br. d, J = 11 Hz, C**H**OH), 3.40 (1H, br. d, J = 14 Hz, ArCH_2), 2.76 (1H, dd, J = 11, 14 Hz, ArCH_2), 2.50-2.20 (4H, complex), 2.00-1.70 (5H, complex), 1.24 (3H, s, CH_3); hrms M^+: 312.1732 (calcd. for $C_{20}H_{24}O_3$: 312.1726).

2-Carbomethoxy-4-[1-methoxycarbonyloxy-2-(4-methoxy-1-naphthyl)ethyl]-4-methylcyclohexanone (45)



The general procedure for carbomethoxylation was used for the preparation of compounds **45**. Treatment of **44** (160 mg, 0.51 mmol) with sodium hydride (36 mg, 1.53 mmol) and dimethyl carbonate (10 ml) under reflux for 30 min gave keto esters **45** (165 mg, 75%): ir (CH_2Cl_2 cast) 2954, 1746 (C=O, ester and carbonate), 1687 (C=O, ketone), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture exists mostly in the enol form and shows only a single set of signal, δ: 12.18 (1H, s, O**H**, enol), 8.29 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 7.91 (1H, br. d, J = 8 Hz, Ar**H**), 7.54 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.47 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.25 (1H, d, J = 8 Hz, Ar**H**), 6.72 (1H, d, J = 8 Hz, Ar**H**), 4.95 (1H, dd, J = 2.5, 10.5 Hz, $CHOCO_2CH_3$), 3.98 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.44 (1H, dd, J = 2.5, 14.5 Hz, $ArCH_2$), 3.39 (3H, s, OCH_3), 3.13 (1H, dd, J = 10.5, 14.5 Hz, $ArCH_2$), 2.40-1.17 (4H, complex), 1.77-1.60 (2H, complex), 1.15 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 196.6 (p), 184.1 (p), 176.6 (p), 173.0 (p), 171.4 (p), 155.4 (p), 154.8 (p), 133.0 (p), 127.6 (a), 126.5 (a), 126.0 (p), 125.6 (p), 124.9 (a), 123.2 (a), 122.7 (a), 114.9 (p), 103.2 (a), 95.2 (p), 83.8 (a), 55.5 (a), 54.5 (a), 51.5 (a), 36.5 (p), 32.3 (p), 31.6 (p), 29.3 (p), 25.8 (p), 18.9 (a); hrms M^+: 428.1836 (calcd. for $C_{24}H_{28}O_7$: 428.1835).

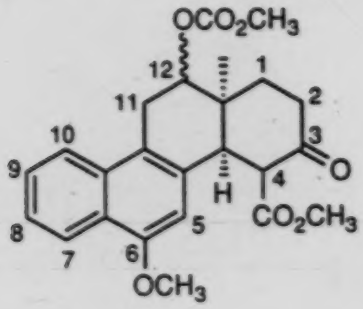
2-Carbomethoxy-4-[1-methoxycarbonyloxy-2-(4-methoxy-1-naphthyl)ethyl]-4-methyl-2-cyclohexenone (40)



Compounds **40** were prepared according to the general procedure for DDQ oxidation. Oxidation of **45** (110 mg, 0.26 mmol) with DDQ (170 mg, 0.78 mmol) for 30 min in dry benzene furnished enone esters **40** (82 mg, 75%): ir (CH_2Cl_2 cast) 2953, 1747 (C=O, ester and carbonate), 1658 ((C=O, ketone), 1617 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture was composed of two diastereoisomers in a ratio of 6:1 and most of their signals were coincidentally overlapped, δ: 8.30 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 8.00 (0.15H, br. d, J = 8 Hz, Ar**H**, minor), 7.88 (0.85H, br. d, J = 8 Hz, Ar**H**, major), 7.56 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.51 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.45 (1H, s, C**H**=CCO), 7.25 (0.85H, d, J = 8 Hz, Ar**H**, major), 7.21 (0.15H, d, J = 8 Hz, Ar**H**, minor), 6.73 (0.85H, d, J = 8 Hz, Ar**H**, major), 6.69 (0.15H, d, J = 8 Hz, Ar**H**, minor), 5.13 (1H, dd, J = 3, 10 Hz, $CHOCO_2CH_3$), 4.00 (3H, s, OCH_3), 3.84 (2.55H, s, OCH_3, major), 3.73 (0.45H, s, OCH_3, minor), 3.58 (0.45H, s, OCH_3, minor), 3.45 (2.55H, s, OCH_3, major), 3.44 (1H, dd, J = 3, 14 Hz, $ArCH_2$), 3.13 (1H, dd, J = 10, 14 Hz, $ArCH_2$), 2.78-2.58 (2H, complex), 2.35 (1H, ddd, J = 5.5, 10, 13.5 Hz,

CH_2), 1.97 (1H, ddd, J = 5.5, 5.5, 12.5 Hz, CH_2), 1.41 (2.55H, s, CH_3, major), 1.34 (0.45H, s, CH_3, minor); ^{13}C APT nmr ($CDCl_3$, 75 MHz) the mixture showed only one set of signals, δ: 193.7 (p), 166.2 (p), 164.8 (p), 158.7 (a), 155.1 (p), 132.7 (p), 132.3 (p), 128.5 (a), 127.9 (a), 126.9 (a), 126.1 (p), 125.1 (a), 124.3 (p), 122.9 (a), 103.2 (a), 81.7 (a), 55.5 (a), 54.8 (a), 52.4 (a), 41.3 (p), 34.6 (p), 32.9 (p), 29.7 (p), 21.4 (a); hrms M^+: 426.1677 (calcd. for $C_{24}H_{26}O_7$: 426.1679).

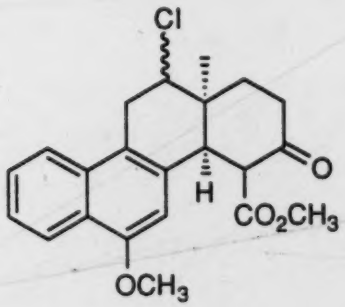
(4aS*, 12aS*)-4-Carbomethoxy-12-methoxycarbonyloxy-3-hydroxy-6-methoxy-12a-methyl-1,2,4a,11,12,12a-hexahydrochrysene (46)



A mixture of **40** (8 mg, 0.02 mmol) in diethyl ether (5 mL) was treated with aluminum chloride (4 mg, 0.03 mmol) at room temperature for 2 h. After workup and purification as described above for cyclization, the crude product gave a diastereoisomeric mixtrue of **46** (7.5 mg, 95%): ir (CH_2Cl_2 cast) 2953, 1745 (C=O, ester and carbonate), 1649 (C=O, enol), 1597 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the inseparable mixture was shown to exist mostly in the enol form and composed of two diastereoisomers (6:1 ratio), of which most of the signals were overlapped, δ: 12.63 (0.85H, s, OH, major), 12.52 (0.15H, s, OH, minor), 8.27 (0.15H, br. d, J = 8 Hz, ArH, minor), 8.22 (0.85H, dd, J = 1.5, 8

Hz, ArH, major), 7.85 (1H, br. d, J = 8 Hz, ArH), 7.53 (1H, ddd, J = 1.5, 8, 8 Hz, ArH), 7.45 (1H, ddd, J = 1.5, 8, 8 Hz, ArH), 6.48 (0.85H, s, ArH, major), 6.40 (0.15H, s, ArH, minor), 5.16 (0.15H, dd, J = 7, 11 Hz, $CHOCO_2CH_3$, minor), 5.04 (0.85H, dd, J = 2, 4.5 Hz, $CHOCO_2CH_3$, major), 4.08 (1H, br. s, ring junction H), 3.92 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.39 (0.85H, dd, J = 2, 2 Hz, $ArCH_2$, major), 3.34 (0.85H, dd, J = 2, 4.5 Hz, $ArCH_2$, major), 3.00 (0.15H, dd, J = 11, 13 Hz, $ArCH_2$, minor), 2.51-2.17 (2H, complex), 1.79 (1H, complex), 1.40 (1H, complex), 1.25 (0.45H, s, CH_3, minor), 1.16 (2.55H, s, CH_3, major); hrms M^+: 426.1673 (calcd. for $C_{24}H_{26}O_7$: 426.1679).

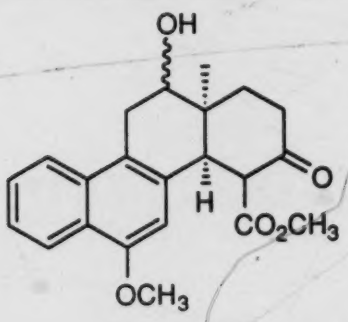
(4aS*, 12aS*)-4-Carbomethoxy-12-chloro-3-hydroxy-6-methoxy-12a-methyl-1,2,4a,11,12,12a-hexahydrochrysene (47)



Following the general procedure, compounds **47** were obtained after treatment of **40** (8.3 mg, 0.02 mmol) with stannic chloride (0.003 mL, 0.03 mmol) in dichloromethane (2 mL) at room temperature for 1 day (3.6 mg, 43%): ir (CH_2Cl_2, cast) 2952, 1746 (C=O, ester), 1651 (C=O, enol), 1601 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the inseparable mixture was observed to exist mostly in their enol forms and composed of two diastereoisomers in 1:1 ratio, δ: 12.64 (0.5H, s, OH, enol), 12.55 (0.5H, s, OH, enol), 8.27 (0.5H, d, J = 8 Hz, ArH), 8.23

(0.5H, d, J = 8 Hz, ArH), 7.83 (0.5H, d, J = 8 Hz, ArH), 7.75 (0.5H, d, J = 8 Hz, ArH), 7.54 (1H, complex, ArH), 7.44 (1H, complex, ArH), 6.57 (0.5H, s, ArH), 6.52 (0.5H, s, ArH), 4.95 (0.5H, dd, J = 7, 12 Hz, CHCl), 4.43 (0.5H, dd, J = 2, 5 Hz, CHCl), 4.16 (1H, s, ring junction H), 3.95 (4.5H, s, OCH_3), 3.90 (1.5H, s, OCH_3), 3.88 (0.5H, br. d, J = 2 Hz, $ArCH_2$), 3.60 (1H, complex, $ArCH_2$), 3.41 (0.5H, dd, J = 2, 5 Hz, $ArCH_2$), 2.61-2.06 (2H, complex), 1.89 (1H, complex), 1.65 (1H, complex), 1.41 (1.5H, s, CH_3), 1.28 (1.5H, s, CH_3); hrms M^+: 386.1288 (calcd. for $C_{22}H_{23}O_4{}^{35}Cl$: 386.1285).

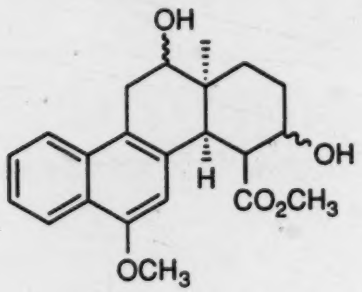
(4aS*, 12aS*)-4-Carbomethoxy-12-hydroxy-6-methoxy-12a-methyl-3-oxo-1,2,3,4,4a,11,12,12a-octahydrochrysene (48)



Sodium methoxide (10 mg, 0.19 mmol) was added to a solution of keto esters **46** (80 mg, 0.19 mmol) in MeOH (10 mL). The mixture was refluxed for 7 h and then neutralized with 10% HCl and concentrated in vacuo. The resulting mixture was dissolved in ethyl acetate (10 mL) and washed with water, brine, dried over magnesium sulfate and concentrated. The residue was purified on silica gel using ethyl acetate/hexane (50:50) as the eluent to give the alcohol mixture **48** (55 mg, 80%): ir (CH_2Cl_2 cast) 3457 (OH), 3071 (Ar-H), 1741 (C=O, ester), 1709 (C=O, ketone), 1644 (C=O, enol), 1624 (C=C) cm^{-1}; ^1H nmr

($CDCl_3$, 300 MHz) the diastereoisomers in the mixture existed mostly in their keto ester forms and in a ratio of 6:1. For major isomer, δ: 8.24 (1H, d, J = 8 Hz, ArH), 7.90 (1H, d, J = 8 Hz, ArH), 7.56 (1H, ddd, J = 1.5, 8, 8 Hz, ArH), 7.48 (1H, ddd, J = 1.5, 8, 8 Hz, ArH), 6.54 (1H, s, ArH), 4.60 (1H, dd, J = 7, 10 Hz, CHOH), 3.97 (1H, complex), 3.91 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.66 (1H, d, J = 7 Hz, $CHCO_2CH_3$), 2.85 (1H, dd, J = 10, 15 Hz, $ArCH_2$), 2.64 (1H, dd, J = 7, 15 Hz, $ArCH_2$), 2.49 (2H, complex), 1.72 (1H, ddd, J = 4.5, 14, 14 Hz, CH_2), 1.30 (1H, complex), 0.98 (3H, s, CH_3); hrms M^+: 368.1626 (calcd. for $C_{22}H_{24}O_5$: 368.1624).

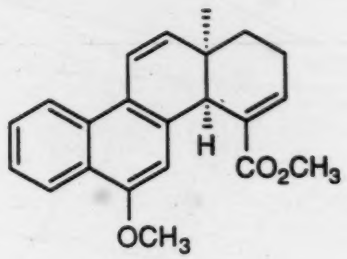
(4aS*, 12aS*)-4-Carbomethoxy-3,12-dihydroxy-6-methoxy-12a-methyl-1,2,3,4,4a,11,12,12a-octahydrochrysene (50)



To an ice cold solution of **48** (24 mg, 0.07 mmol) in MeOH/THF (10 mL, 1:1) was added $NaBH_4$ (3.0 mg, 0.07 mmol). After stirring for 1 h at 0°C, the reaction mixture was concentrated, the residue was dissolved in ethyl acetate (10 mL) and washed with water and brine. The organic layer was then dried over magnesium sulfate, filtered and evaporated. Flash chromatography (50% ethyl acetate/hexane) gave the mixture **50** (21 mg, 87%): ir (CH_2Cl_2 cast) 3439

(OH), 3070 (Ar-H), 1729 (C=O, ester), 1624 (C=C) cm^{-1}; hrms M^+: 370.1785 (calcd. for $C_{22}H_{26}O_5$: 370.1781).

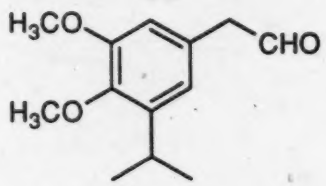
(4aR*, 12aS*)-4-Carbomethoxy-6-methoxy-12a-methyl-1,2,4a,12a-tetrahydrochrysene (49)



Triethylamine (0.05 mL, 0.36 mmol) was added to a solution of **50** (21 mg, 0.06 mmol) and DMAP (catalytic amount) in THF (5 mL) at 0°C, followed by methanesulfonyl chloride (0.02 mL, 0.18 mmol), and the reaction mixture was stirred for 3 h at 0°C. It was filtered, the insoluble material was washed with cold THF (5 mL), and the filtrate was concentrated in vacuo. The crude product was then dissolved in dry benzene (5 mL), and DBU (0.05 mL, 0.33 mmol) was added. After being refluxed for 2 h, the reaction mixture was cooled to room temperature and water was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (3x5 mL), and the combined organic layers were washed with water, brine and dried over magnesium sulfate. Concentration gave a residue which was chromatographed (20% ethyl acetate/hexane) to afford compound **49** (8 mg, 43%): ir (CH_2Cl_2 cast) 2924, 1716 (C=O, ester), 1615 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 8.20 (1H, dd, J = 1.5, 8 Hz, Ar**H**), 8.06 (1H, br. d, J = 8 Hz, Ar**H**), 7.49 (1H, ddd, J = 1.5, 8, 8

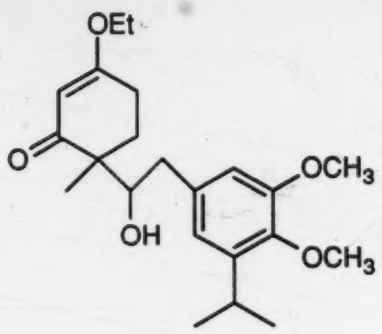
Hz, Ar**H**), 7.41 (1H, ddd, J = 1.5, 8, 8 Hz, Ar**H**), 7.13 (1H, d, J = 10 Hz, ArC**H**=CH), 7.07 (1H, dd, J = 3.5, 3.5 Hz, C**H**=CCO$_2$CH$_3$), 6.60 (1H, s, Ar**H**), 5.88 (1H, d, J = 10 Hz, ArCH=C**H**), 3.95 (3H, s, OC**H**$_3$), 3.88 (1H, br. s, ring junction **H**), 3.74 (3H, s, OC**H**$_3$), 2.28 (2H, complex, C2-**H**), 1.70 (1H, complex), 1.37 (1H, complex), 1.13 (3H, s, C**H**$_3$); hrms M$^+$: 334.1565 (calcd. for $C_{22}H_{22}O_3$: 334.1569).

2-(3-isopropyl-4,5-Dimethoxyphenyl)acetaldehyde (53)



A mixture of 2-(3-isopropyl-4,5-dimethoxyphenyl)ethanol (730 mg, 3.25 mmol) and PCC (2.1 g, 9.75 mmol) in dichloromethane (20 mL) was stirred for 2 h at room temperature. The reaction mixture was filtered through a Florisil column, and the filtrate was concentrated in vacuo to give the aldehyde **53** (614 mg, 85%): ir (CH_2Cl_2 cast) 3427 (OH, enol), 2730, 1726 (C=O, aldehyde), 1588 (C=C) cm^{-1}; ^{1}H nmr ($CDCl_3$, 300 MHz) 9.74 (1H, t, J = 2.5 Hz, C**H**O), 6.67 (1H, d, J = 2 Hz, Ar**H**), 6.58 (1H, d, J = 2 Hz, Ar**H**), 3.85 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 3.62 (2H, d, J = 2.5 Hz, C**H**$_2$), 3.34 (1H, sept, J = 7 Hz, Me$_2$C**H**), 1.20 (6H, d, J = 7 Hz, C**H**$_3$); hrms M$^+$: 222.1254 (calcd. for $C_{13}H_{18}O_3$: 222.1256)

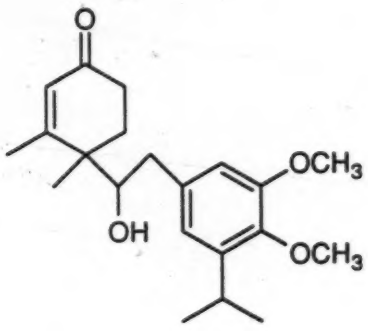
3-Ethoxy-6-[1-hydroxy-2-(3-isopropyl-4,5-dimethoxyphenyl)ethyl]-6-methyl-2-cyclohexenone (54)



Following the procedure as described for the preparation of **42** above, enone **41** (421 mg, 2.73 mmol) was subjected to aldol condensation with LDA (3.28 mmol) and aldehyde **53** (600 mg, 2.70 mmol) in THF (10 mL) at -78°C for 1 h to afford the alcohols **54** (860 mg, 85%): ir (CH_2Cl_2 cast) 3430 (OH), 2961, 1643 (C=O, enone), 1607 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture was composed of two inseparable diastereoisomers in a ratio of 3:1, δ: 6.68 (0.75H, d, J = 2 Hz, Ar**H**, major), 6.67 (0.75H, d, J = 2 Hz, Ar**H**, major), 6.66 (0.25H, d, J = 2 Hz, Ar**H**, minor), 6.64 (0.25H, d, J = 2 Hz, Ar**H**, minor), 5.30 (0.25H, d, J = 1 Hz, C=C**H**CO, minor), 5.25 (0.75H, d, J = 1 Hz, C=C**H**CO, major), 4.07 (0.25H, dd, J = 2, 10 Hz, C**H**OH, minor), 4.02 (0.75H, dd, J = 2, 10 Hz, C**H**OH, major), 3.90 (2H, q, J = 7 Hz, CH_3CH_2O), 3.84 (2.25H, s, OCH_3, major), 3.83 (0.75H, s, OCH_3, minor), 3.77 (3H, s, OCH3), 3.30 (1H, sept, J = 7 Hz, Me_2CH), 2.75 (0.25H, dd, J = 2, 14 Hz, $ArCH_2$, minor), 2.69 (0.75H, dd, J = 2, 14 Hz, $ArCH_2$, major), 2.51 (1H, dd, J = 10, 14 Hz, $ArCH_2$), 2.47-2.30 (2H, complex), 2.00-1.60 (2H, complex), 1.35 (3H, t, J = 7 Hz, CH_3CH_2O), 1.23 (3H, s, CH_3), 1.18 (6H, dd, J = 1, 7 Hz, $(CH_3)_2CH$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) two sets of signals were found; for the major isomer, δ: 206.0 (p), 176.8 (p), 152.4 (p), 144.8 (p), 142.1 (p), 135.3 (p), 119.0 (a), 110.8 (a), 101.5 (a), 76.8 (a), 64.5 (p), 60.9 (a), 55.8 (a), 46.5 (p), 37.7 (p), 29.4 (p), 26.9 (a), 25.9 (p), 23.6 (a), 19.7 (a), 16.9 (a), 14.2 (a);

for minor isomer, δ: 204.3 (p), 176.7 (p), 152.5 (p), 144.8 (p), 142.2 (p), 135.2 (p), 118.9 (a), 110.8 (a), 102.0 (a), 76.3 (a), 64.4 (p), 60.9 (a), 55.7 (a), 48.0 (p), 37.4 (p), 29.4 (p), 26.9 (a), 25.9 (p), 23.6 (a), 19.7 (a), 16.9 (a), 14.2 (a); hrms M^+: 376.2245 (calcd. for $C_{22}H_{32}O_5$: 376.2250).

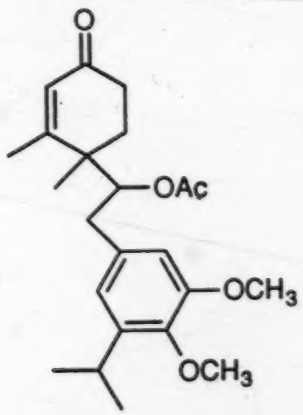
4-[1-Hydroxy-2-(3-isopropyl-4,5-dimethoxyphenyl)ethyl]-3,4-dimethyl-2-cyclohexenone (55)



A solution of **54** (220 mg, 0.58 mmol) in THF (10 mL) was stirred and cooled at -78°C as methyllithium (1.25 mL, 1.74 mmol) was added dropwise. After 45 min, the reaction mixture was warmed up to 0°C, and water (5 mL) was added slowly to destroy excess methyllithium. The resulting mixture was then hydrolyzed with 10% HCl (10 mL) at room temperature for 1 h. The aqueous solution was extracted with ether (3x10 mL). The combined organic extracts were washed with water (20 mL) and saturated NaCl (20 mL), dried over magnesium sulfate and concentrated. Purification by flash chromatography with ethyl acetate/hexane (50:50) as eluent produced enones **55** (194 mg, 96%): ir (CH_2Cl_2 cast) 3431 (OH), 1666 (C=O, enone), 1611 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz) the mixture of two diastereoisomers showed only one

set of signals, δ: 6.46 (1H, d, J = 2 Hz, ArH), 6.59 (1H, d, J = 2 Hz, ArH), 5.95 (1H, d, J = 1 Hz, C=CHCO), 3.94 (1H, br. d, J = 10.5 Hz, CHOH), 3.86 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.34 (1H, sept, J = 7 Hz, Me_2CH), 2.71 (1H, dd, J = 2, 13.5 Hz, $ArCH_2$), 2.57 (1H, dd, J = 10, 13.5 Hz, $ArCH_2$), 2.50 (2H, complex), 2.14 (1H, complex) 2.07 (3H, s, $CH_3C=CH$), 1.98 (1H, complex), 1.67 (1H, d, J = 3.5 Hz, OH), 1.32 (3H, s, CH_3), 1.21 (6H, d, J = 7 Hz, $(CH_3)_2CH$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) a single set of signals was observed for the mixture, δ: 199.0 (p), 167.1 (p), 152.9 (p), 145.3 (p), 142.9 (p), 134.2 (p), 128.4 (a), 118.8 (a), 110.6 (a), 77.8 (a), 61.0 (a), 55.8 (a), 42.9 (p), 39.4 (p), 34.0 (p), 30.1 (p), 26.9 (a), 23.6 (a), 23.5 (a), 21.4 (a), 21.0 (a); hrms M^+: 346.2147 (calcd. for $C_{21}H_{30}O_4$: 346.2144).

4-[1-Acetoxy-2-(3-isopropyl-4,5-dimethoxyphenyl)ethyl]-3,4-dimethyl-2-cyclohexenone (57)



Using pyridine and acetic anhydride, the general procedure for acetylation was applied to convert enones **55** (190 mg, 0.55 mmol) to acetates **57** (202 mg, 95%): ir (CH_2Cl_2 cast) 2961, 1743 (C=O, ester), 1674 (C=O, enone), 1617

(C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the mixture of two diastereoisomers displayed only a single set of signals, δ: 6.59 (1H, d, J = 2 Hz, ArH), 6.53 (1H, d, J = 2 Hz, ArH), 5.91 (1H, d, J = 1 Hz, C=CHCO), 5.49 (1H, dd, J = 2.5, 10 Hz, CHOAc), 3.85 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 3.31 (1H, sept, J = 7 Hz, Me_2CH), 2.79 (1H, dd, J = 10, 14.5 Hz, $ArCH_2$), 2.63 (1H, dd, J = 2.5, 14.5 Hz, $ArCH_2$), 2.47 (2H, complex), 2.25 (1H, complex), 2.03 (3H, d, J = 1 Hz, CH_3C=CH), 1.96 (3H, s, CH_3CO_2), 1.92 (1H, complex), 1.22 (3H, s, CH_3), 1.18 (3H, d, J = 7 Hz, $(CH_3)_2CH$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) the mixture revealed only one set of signals, δ: 198.5 (p), 170.0 (p), 164.3 (p), 152.5 (p), 145.1 (p), 142.3 (p), 133.2 (p), 129.1 (a), 118.9 (a), 110.3 (a), 78.0 (a), 61.0 (a), 55.8 (a), 43.0 (p), 37.1 (p), 33.7 (p), 29.3 (p), 26.7 (a), 23.6 (a), 23.5 (a), 21.8 (a), 20.9 (a), 20.5 (a); hrms M^+: 388.2254 (calcd. for $C_{23}H_{32}O_5$: 388.2250).

CHAPTER TWO

Application to the synthesis of thiophene-containing compounds

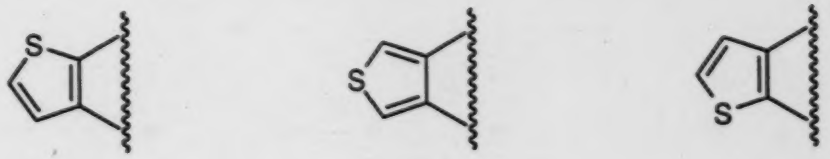
INTRODUCTION

The chemistry of polycyclic thiophene-containing compounds is one of the interesting branches of organic chemistry. It is interesting in terms of synthetic procedures and pharmacological significance.

The incorporation of the thiophene moiety into biologically active compounds has continued unabated during the past 15 years.[35] The discovery and development of pharmaceutically active molecules have been guided not only by classical medicinal chemistry but also by new biochemical assays. New concepts of therapy such as the use of enzyme inhibitors to control disease states have increased the scope of medicinal chemical research. The continued need to develop agents with increased potency and activity as well as greater specificity and reduced toxicity has driven medicinal and agricultural chemical research. As a consequence, many new thiophene derivatives were synthesized, and numerous insights into their modes of action as biological agents have been gained.

The significance of biologically active thiophene derivatives can be illustrated by two prominent published reviews. Drehsen and Engel in 1983 published a detailed article explaining the structure-activity relationships that have been developed for various thiophene series.[36] In this report, thiophene derivatives acting in the central nervous system and the cardiovascular system were discussed. Bohm in 1984 updated his previous excellent review of synthetic and pharmacological aspects of thiophene structure.[37]

There are a variety of reasons why thiophene derivatives are interesting to the pharmaceutical chemists. But the main interest is in its structural advantage as compared to other benzene derivatives. Certainly, the need to develop complete structure-activity relationships in any series requires investigation into the steric and electronic requirements of aromatic moieties in such molecules. Thiophene, with its six-π electron aromaticity, is electronically and sterically similar to benzene. As a result, thiophene analogs of biologically active benzene derivatives may well exhibit similar activities. In fact, the electron-rich properties as well as the slightly smaller steric volume of thiophene as compared to benzene may play an important role in fitting the necessary biological receptor sites. At the same time, the presence of a heteroatom or the lower resonance energy in thiophene may alter its metabolic fate, and thus, the thiophene derivatives may have less toxic effects and/or a better therapeutic profile. This concept of bioisosterism was initially proposed by Erlenmeyer[38] and was further elaborated recently by both Thornber and Bohm.[39]

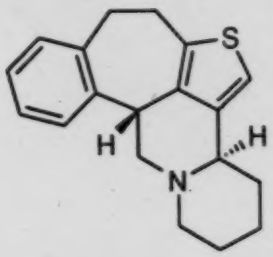


2,3- 3,4- 3,2-

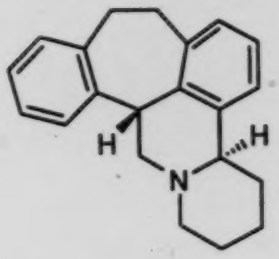
Scheme 41

Fundamentally, the thiophene moiety has been incorporated into biologically active molecules in two manners. Firstly, thiophene can be used in the replacement of pendant aromatic rings on biologically important molecules.

Though simple, this procedure is important to the development of structure-activity relationships in aryl-substituted systems. Secondly and more chemically challenging is the synthesis of molecules containing thiophene either as the central ring or as part of the central fused ring system. In such systems, synthesis of the three possible 2,3-, 3,4- and 3,2-isomeric substitution patterns clearly provides greatest challenge to the synthetic organic chemist (Scheme 41). Such synthetic targets provide the utmost insight into the effect of thiophene on biological targets. Many biological agents of this type have been prepared, based upon active benzene derivatives. For instance, QM 7184 (**59**),



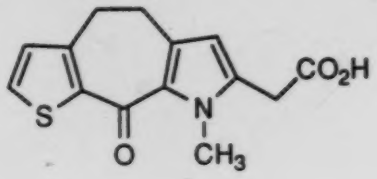
59



60

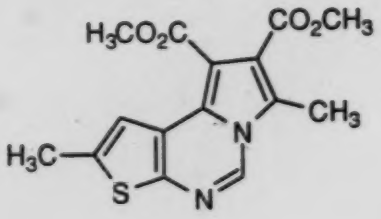
the thiophene isostere of taclamine (**60**) a psychotropic agent exhibiting actions characteristic of anti-anxiety drugs in experimental animals,[40] was synthesized[41] and reported to be a neuroleptic agent. In addition to its neuroleptic profile, compound **59** had high affinity for rat cortical and striatal α-adrenergic receptors. These affinities may play a role in treatment of schizophrenia, and the compound's properties have been summarized.[42] Though promising, molecules based less upon benzene isostere have been prepared in recent years to investigate inherent properties. Such example is demonstrated with compound **61**, a new anti-inflammatory and analgesic agent

which was prepared in 1983 by Rosenberg and Ward.[43] Although the thienocycloheptapyrrole **61** possessed anti-inflammatory and analgesic properties, these were not sufficient to warrant progression to the clinic.



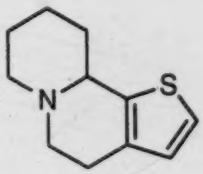
61

In the on going search for potential medicinal agents, many polycyclic thiophene-containing compounds have been synthesized and investigated for treatment of central nervous system disorder, metabolic disease, infectious disease and so on.[35] Among all, tricyclic thiophene derivatives constituted a large class of compounds which showed pharmacologically interesting activities. In this context, compound **62** was synthesized *via* cycloaddition process in 1988 by New and coworkers.[44] The impetus for the synthesis of this molecule is the development of anti-anxiety drugs that have a cleaner side-effect profile. Based on biological evaluation, compound **62** was found to



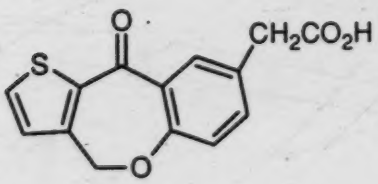
62

have potent binding affinity for the benzodiazepine receptor, albeit slightly less than half that of diazepam. The need for new modes of treating hypertension have led to strong growth in anti-hypertensive agents. As a result, there have been numerous efforts at developing agents that are more selective as well as investigating compounds with a novel mechanism of action. In this regard, compound **63** was among the most potent in a series of arylquinolizines studied as antihypertensive agents.[45] In the paper reported by Huff and coworkers,[45] compound **63** was prepared in a short manner and showed a binding affinity at all subtypes of α-receptor through hydrophobic interaction due to the aromatic ring.

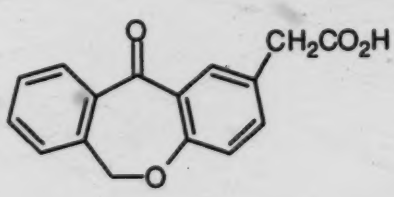


63

In the development of new drugs for treatment of inflammation, compound **64** was synthesized and evaluated for anti-inflammatory activity in rats.[46] It was observed that compound **64** was two times more active than its carbocyclic

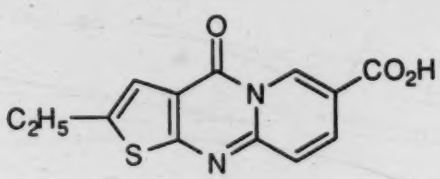


64



65

analogue **65** although its gastric irritation liability in rats was determined approximately 2.5 times more irritating than **65**. Furthermore, a great deal of research has gone into developing orally active antiallergy agents since disodium cromoglycate (DSCG), the drug currently available for the prophylactic treatment of bronchial asthma, is not active orally. Thus, a series of thienopyrimidines was prepared and evaluated for antiallergy activity.[47] Several of these compounds were shown to have potent oral activity and were superior to disodium cromoglycate. Among these compounds, **66** was revealed as one of the two most orally active anti-allergy agents.

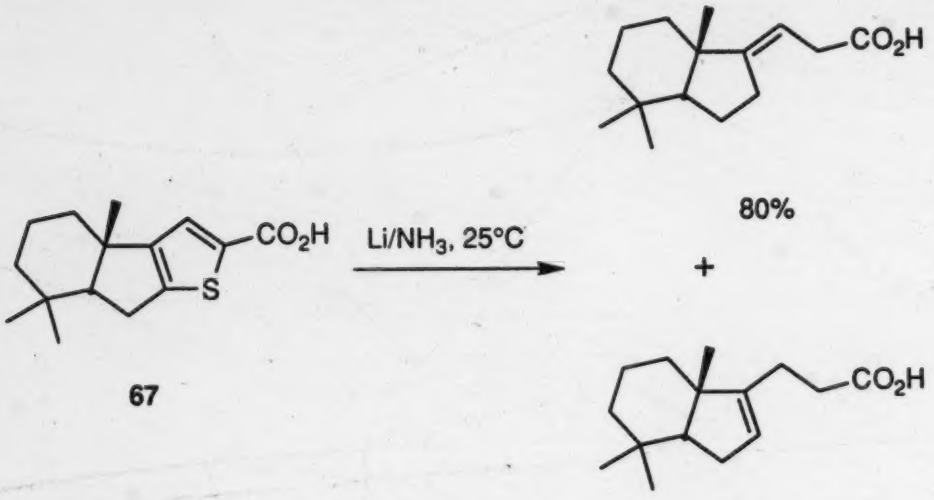


66

In short, as the number of sensitive biologic probes expands in connection with the increasing sophistication of medical and biochemical research, there are more opportunities to incorporate thiophene with its unique physicochemical properties into potential drug candidates. Thienyl [2,3]-, [3,4]-, and [3,2]-fused molecules all have good activities, and the issue of which isomeric system will have superior remains unpredictable.

Despite all the biologic profile, polycyclic thiophene fused compounds have been constructed as useful intermediates for the transformations into compounds of various classes. Owing to the method of reductive

desulfurization, the transformation was described by Semenovskii and Ernel'yanove[48] for tricyclic acid **67** when lithium was used in liquid ammonia at

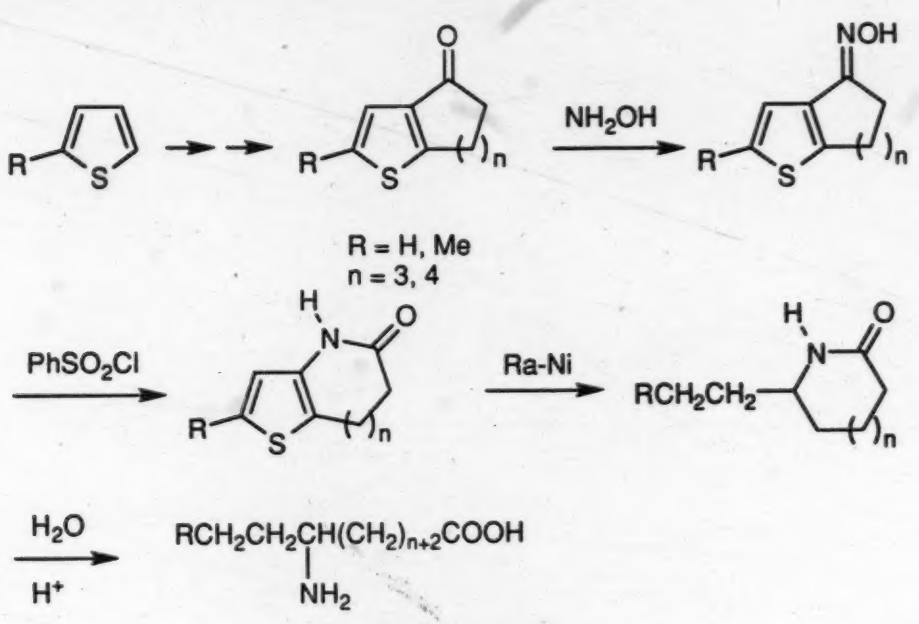


67

Scheme 42

25°C under pressure (Scheme 42), in which substituted thiophenecarboxylic acid **67** underwent hydrogenolysis of the C-S bond and products that did not contain sulfur were formed. More interestingly, the synthesis of lactams from a series of simple thiophenes was developed by Gol'dfarb.[49] These lactams were later transformed into amino acids by the technique based on reductive desulfurization with Raney Nickel (Scheme 43). According to this scheme, thiophene or 2-methylthiophene used as starting material was transformed into bicyclic ketones, oximes which underwent Beckmann rearrangement. Using the action of benzenesulfonyl chloride, there were obtained in high yield lactams having the amino group directly attached to the β-position of the

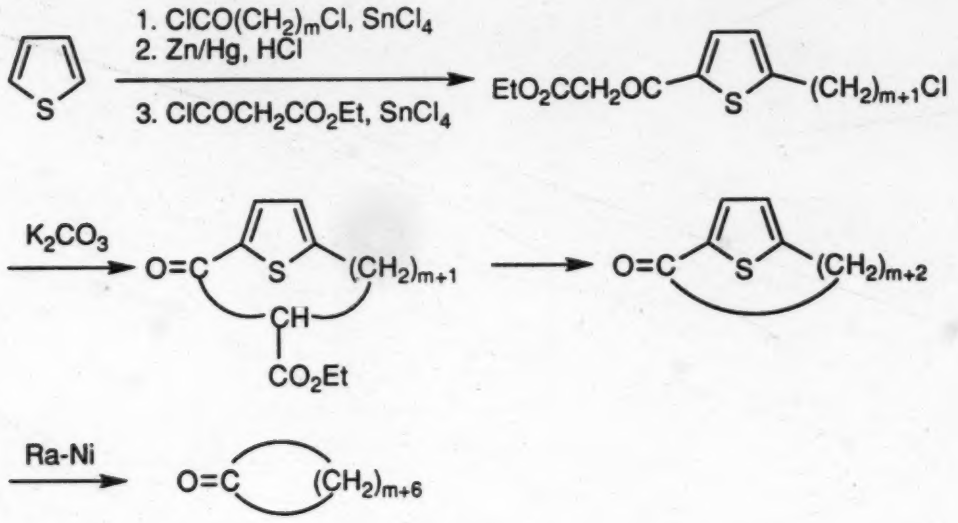
thiophene ring. Reductive desulfurization of these lactams followed by acid hydrolysis led to the corresponding amino acids.



Scheme 43

With the aid of reductive desulfurization of thiophene derivatives, the synthesis of macrocyclic compounds can be achievable *via* the preparation of bi- or polycyclic compounds that possess the thiophene ring followed by the subsequent removal of the sulfur atom serving as a bridge. The advantage of this procedure is that thiophene, with its highly reactive properties, makes the construction of polycyclic systems possible. It is also important to note that because of the aromatic character, thiophene can be utilized for lengthening the carbon chain and incorporating substituents. An example of this use of thiophene is illustrated in Scheme 44.[50]

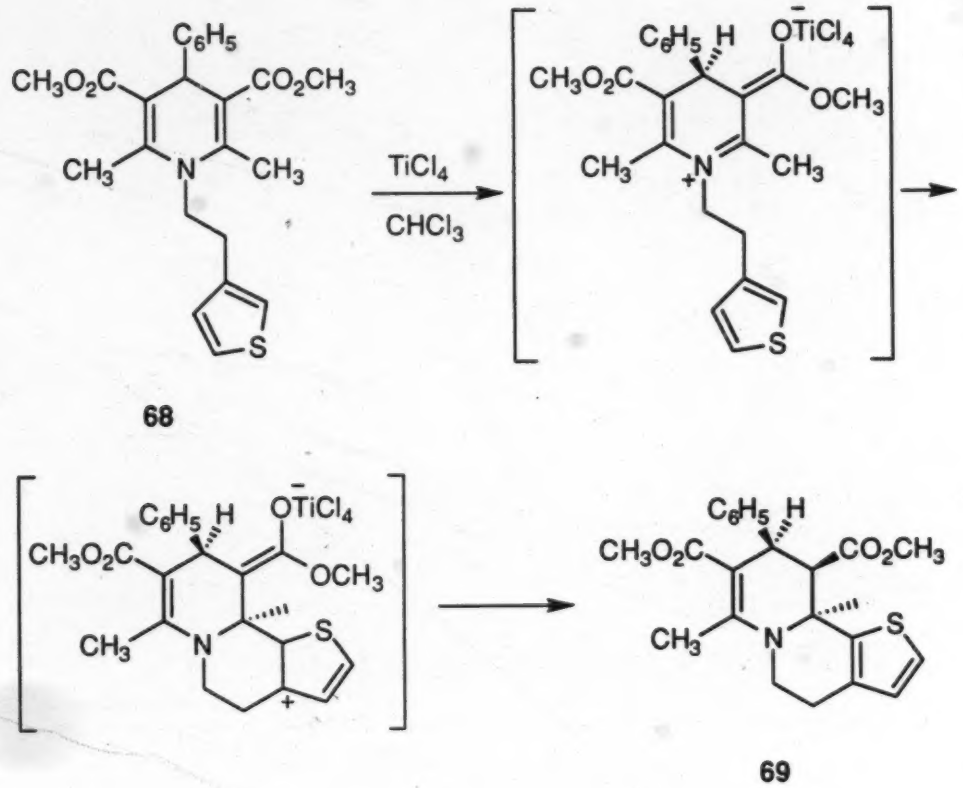
There have been a few cases where thiophene fused polycyclic compounds were prepared *via* polyene cyclizations that were promoted by either Lewis acids or protonated acids. Some of these works centered on the intramolecular trapping of the intermediate iminium ions by the appropriate nucleophilic site of



Scheme 44

the thiophene ring. For instance, in an attempt to prepare dihydropyridine analogues for biological evaluation, Hartman[51] observed that compound **68** underwent cyclization, presumably *via* an iminium intermediate, to produce cyclized product **69** in 73% yield when it was treated with titanium tetrachloride at room temperature for one day (Scheme 45). Also, the thiophene isosteres of the very potent antischistomicide praziquantel **70** were prepared according to a cyclization method that was mediated by the iminium ions

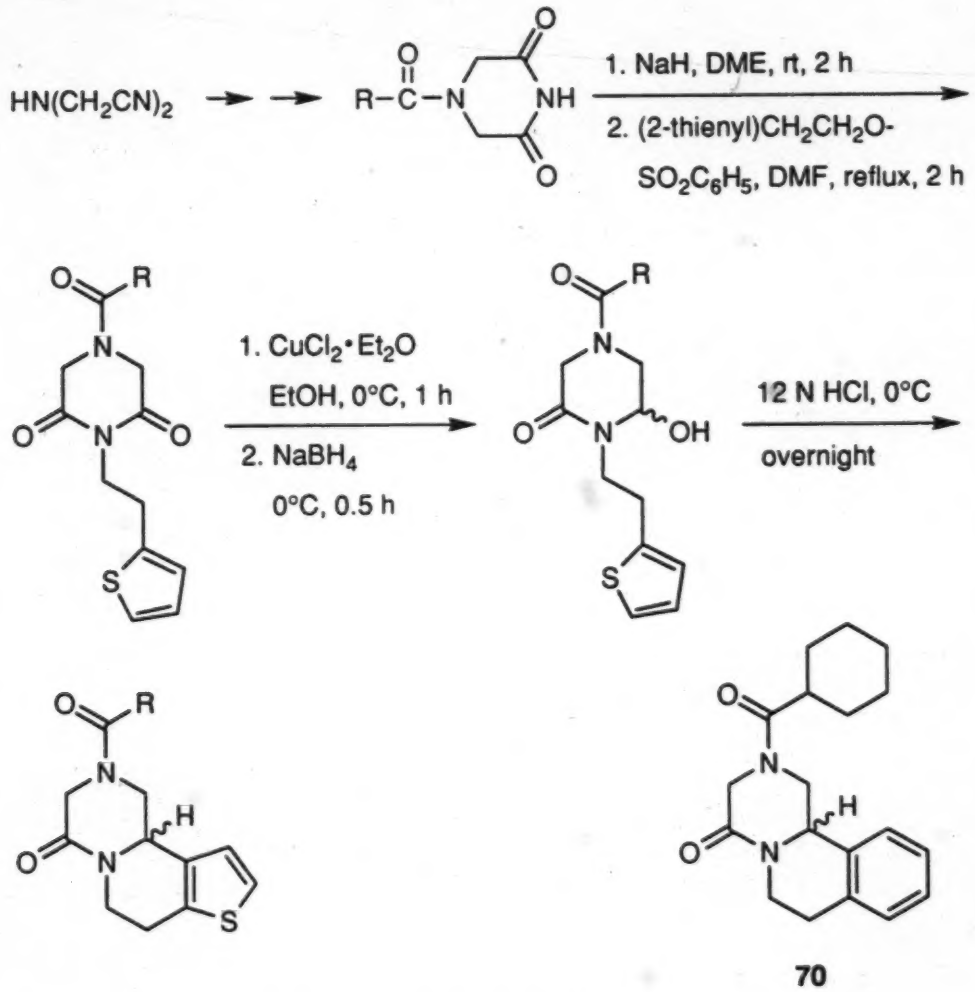
(Scheme 46).[52] However, the biologic profile of these compounds were not reported.



Scheme 45

About two decades ago, Macco extensively investigated both racemic and asymmetric syntheses of thiophene isosteres of 16-thia-D-homoestrogen using an acid-catalyzed ring closure in the hope of improving the antifertility and serum lipid-lowering properties of the steroid.[53] A selected example is illustrated in Scheme 47 by the cyclization of **71**, which was promoted by an

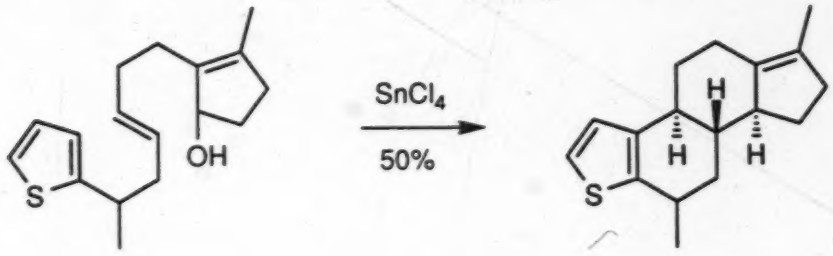
allylic alcohol moiety. Unfortunately, the yields of these transformations were only modest (50%), and their pharmacological activities were not studied.



Scheme 46

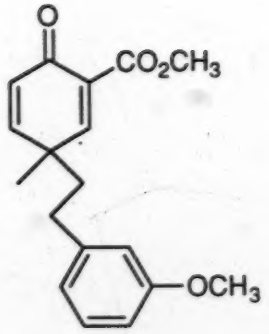
Inspired by our newly developed polyene cyclization, we became interested in the preparation of tricyclic thiophene-containing compounds. From the results described in Chapter One of this thesis, it was shown that the cross

conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclizations, that occurred readily with high regio- and stereoselectivity. Essentially, this cyclization process allows for expeditious construction of *cis*-fused polycyclic compounds with a high degree of functionalization. Therefore, in replacing the aromatic ring in compound **33** with a thiophene nucleus such as that in compound **72**, we could in principle, prepare highly functionalized polycyclic thiophene-containing compounds that could be evaluated for medicinal properties. The results are discussed in the following section.



71

Scheme 47



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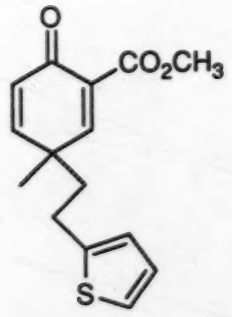
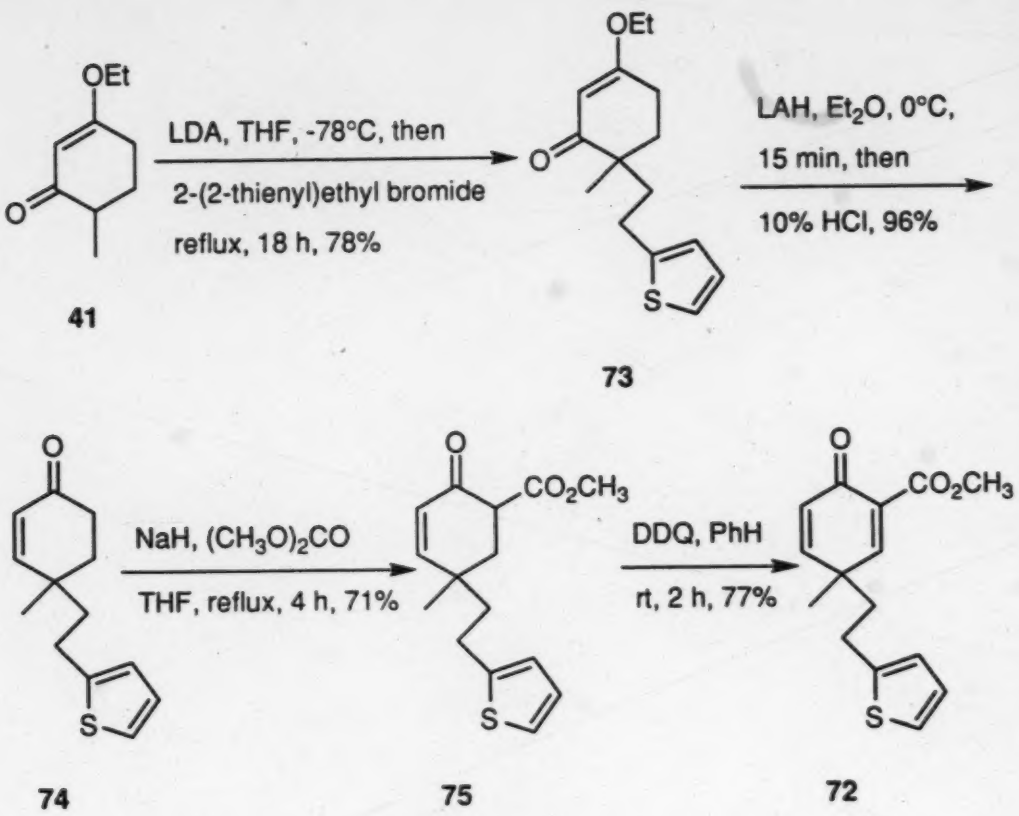


72

RESULTS AND DISCUSSION

Since it was predicted in the literature that all three possible 2,3-, 3,4- and 3,2-isomeric substitution patterns of thiophene fused molecules have good biological activities, the synthesis of all three isomers utilizing our efficient procedure was carefully and successfully explored. Our initial study centered on the preparation of the thiophene 3,2-fused tricyclic compound *via* the polyene cyclization promoted by the cross conjugated β-keto ester system which required compound **72** as the precursor. Thus, the synthesis of **72** was carried out using 3-ethoxy-6-methyl-2-cyclohexenone **41** as the starting material *via* a sequence involving four synthetic operations as shown in Scheme 48.

Stork-Danheiser alkylation of enone **41** with lithium diisopropylamide (LDA) and 2-(2-thienyl)ethyl bromide under reflux for 18 hours followed by flash chromatography gave compound **73** in 78% yield. Compound **73** displayed a molecular ion peak at m/z 264.1188 in the mass spectrum, consistent with the molecular formula $C_{15}H_{20}O_2S$. The elemental analysis was also in agreement with the molecular composition. Its ir spectrum showed the presence of the enone carbonyl group at 1651 cm^{-1}, and in its ^1H nmr spectrum, three aromatic protons were observed at δ 7.91 (dd, J = 1 and 5 Hz), 6.90 (dd, J = 3.5 and 5 Hz) and 6.79 (dd, J = 1 and 3.5 Hz). These assignments were confirmed in the ^{13}C APT nmr spectrum, which also displayed the carbonyl carbon at δ203.4. In the ^1H nmr spectrum, a singlet was also found at δ 5.25 accounting for the vinylic proton, whereas the methyl group alpha to the carbonyl was observed in the high field region at δ 1.14 as a singlet. The reduction of compound **73** was



Scheme 48

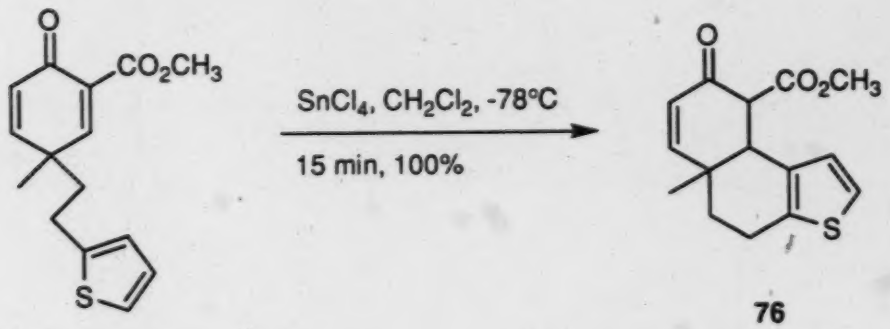
carried out followed by treatment of the crude product with 10% hydrochloric acid to give enone **74** in 96% yield over two steps. The structure of **74** was assigned by spectroscopic methods. The ir spectrum showed a carbonyl absorption at 1680 cm^{-1}, indicating the presence of an enone. In the ^1H nmr spectrum, two doublets at δ 6.71 and 5.91 with the same coupling constant (J = 10 Hz), were attributed to the two vinylic protons of the enone moiety. Three aromatic protons appeared at δ 7.12 (dd, J = 1 and 5 Hz), 6.92 (dd, J = 3.5 and 5 Hz) and 6.80 (dd, J = 1 and 3.5 Hz). The methyl group appeared at δ 1.22 as

a sharp singlet. The high resolution mass spectrum showed a molecular ion peak at m/z 220.0920, corresponding to the molecular formula $C_{13}H_{16}OS$ which was further confirmed by elemental analysis and ^{13}C APT nmr spectroscopy.

Toward the synthesis of **72**, compound **74** was treated with sodium hydride and dimethyl carbonate in refluxing tetrahydrofuran. The desired product **75** thus formed exclusively in 71% yield after 4 hours was shown to exist as a mixture of two keto forms (1:1, 70%) and an enol form (30%), as evidenced by the ^1H nmr spectrum, each of which displayed a single set of unique signals. Its mass spectrum showed a molecular ion peak at m/z 278.0978, consonant with the molecular formula $C_{15}H_{18}O_3S$ which was also supported by the elemental analysis. The ir spectrum confirmed the existence of ketone and ester carbonyl groups, showing absorption bands at 1743 (ester, keto ester form), 1681 (enone, keto ester form) and 1624 cm^{-1} (C=O, ester of enol form). In the ^1H nmr spectrum, the hydroxyl proton of the enol form appeared at δ 11.89 as a sharp singlet. The methyl protons of the ester moiety of both keto and enol forms were shown as a sharp singlet overlapping at δ 3.78, validating the incorporation of the ester functionality. This evidence was further supported by the the signals at δ 3.62 (dd, J = 5 and 14 Hz) and 3.58 (dd, J = 5 and 12 Hz) which were attributed to the α proton of the β-keto ester moiety of the keto epimers.

The second conjugated double bond of enone ester **72** was incorporated using the DDQ oxidation method. Thus, compound **75** was allowed to react with DDQ in benzene at room temperature for 2 hours. The crude product was then purified by flash chromatography to give compound **72** in 77% yield. In the ir

spectrum, two carbonyl absorption bands were displayed at 1741 (ester) and 1665 cm^{-1} (ketone). Also, the ^{13}C APT nmr spectrum showed two signals at δ 181.4 and 165.1 indicating the presence of the keto and ester functionalities, respectively. Its mass spectrum depicted a molecular ion peak at m/z 276.0816 corresponding to the expected formula $C_{15}H_{16}O_3S$. By first order analysis of the ^1H nmr spectrum, the signals of the aromatic protons were observed at δ 7.10 (dd, J = 1 and 5 Hz), 6.88 (dd, J = 3.5 and 5 Hz) and 6.72 (dd, J = 1 and 3.5 Hz), whereas the three olefinic protons were shown at δ 7.50 (d, J = 3 Hz), 6.77 (dd, J = 3 and 10 Hz) and 6.35 (d, J = 10 Hz). The signal of the methyl of the ester moiety was displayed as a singlet at δ 3.83, whereas the quarternary methyl singlet was observed at δ 1.36.

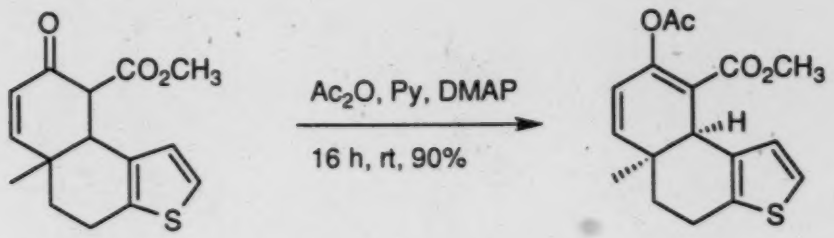


72 **76**

Scheme 49

With enone ester **72** in hand along with the reliable tool for constructing polycyclic compounds which was thoroughly described in chapter 1 of this thesis, we were able to synthesize the thiophene fused tricyclic compound. The particular Lewis acid chosen was stannic chloride because it was observed previously to be appropriate for the related polyene cyclizations. As a result,

when enone ester **72** was treated with stannic chloride in dichloromethane at -78°C for 15 minuites, the tricyclic compound **76** was formed as a single product in quantitative yield (Scheme 49). Compound **76** was found to exist as an inseparable mixture of two keto epimers and an enol tautomer in a ratio of 3:4:3, respectively, as indicated by the ^1H nmr spectrum in which the hydroxyl proton of the enol isomer was shown as a sharp singlet at δ 12.08, while the existence of two keto epimers was indicated by an additional set of signals of sp^2 protons. In its mass spectrum, compound **76** showed a molecular weight of 276.0819 consistent with the molecular formula $C_{15}H_{16}O_3S$. The ir spectrum displayed absorption bands at 1743 (C=O, ester), 1678 (C=O, ketone) and 1654 cm^{-1} (C=O, enol). Although the results discussed in chapter 1 of this thesis intuitively convinced us that this compound was *cis*-fused, evidence must be provided for solid proof and it was not profitable to use spectroscopic methods



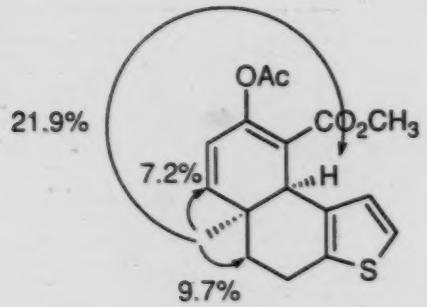
76 **77**

Scheme 50

for stereochemical analysis of **76**. As a consequence, the regiochemistry and stereochemistry of this compound was assigned as follows. Treatment of **76** with acetic anhydride in pyridine gave rise to the corresponding enol acetate **77**

(Scheme 50) whose structure was confirmed by spectroscopic means with the assistance of an NOE experiment.

Thus, in the ir spectrum, compound **77** displayed two carbonyl absorption bands at 1766 (enol acetate) and 1709 cm^{-1} (conjugated ester). The molecular ion peak in accord with the molecular formula of $C_{17}H_{18}O_4S$ was found at m/z 318.0925 in the high resolution mass spectrum. Moreover, compound **77** revealed in the ^{13}C APT nmr spectrum two signals at δ 168.3 and 166.5, assigned to the ester carbonyls. Further confirmation of the structure was derived from the ^1H nmr spectrum in which the signals at δ 7.01 and 6.66 with the same coupling constant (J = 5 Hz) were attributed to the aromatic protons. The two vinylic protons appeared at δ 6.04 (dd, J = 1.5 and 10 Hz) and 5.66 (d, J = 10 Hz), characteristic of *cis*-disubstituted olefin, whereas the ring junction proton was observed at δ 3.80 (d, J = 1.5 Hz), due to deshielding effects from both conjugated double bond and the thiophene ring. A complete set of ^1H nmr spectral data is outlined in Table 4. The *cis* ring junction of compound **77** was



77

Figure 7

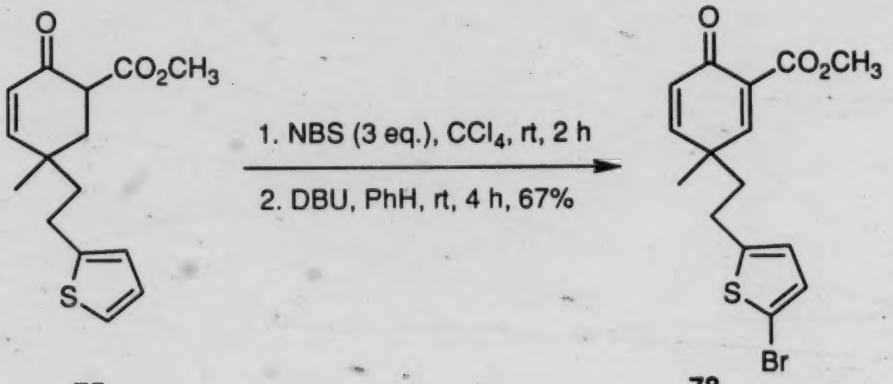
established by NOE experiment. As shown in Figure 7, irradiation of the methyl group at δ 1.23 resulted in enhancements of the ring junction proton (21.9%), adjacent double bond proton at δ 6.04 (7.2%), and the nearby methylene protons at δ 1.95 (9.7%).

Table 4. ^{1}H nmr spectral data of compound **77**

Proton	δ (in ppm)	**Multiplicity** (J in Hz)
Ar**H**	7.01	d (J = 5)
Ar**H**	6.66	d (J = 5)
C**H**=CHCOAc	6.04	dd (J = 1.5, 10)
CH=C**H**COAc	5.66	d (J = 10)
OCH_3	3.84	s
ring junction **H**	3.80	d (J = 1.5)
2 x ArCH_2	2.82	complex
CH_3CO_2	2.22	s
2 x CH_2	1.95	complex
CH_3	1.23	s

An Attempt was also made to introduce the second double bond to compound **75** using the bromination-dehydrobromination protocol.[54] This process has been used successfully in our laboratory on several occasions with similar compounds. In this particular case, when keto ester **75** was treated with *N*-

bromosuccinimide (NBS) in carbon tetrachloride in the dark, a bromine atom was introduced at the alpha position of the keto ester moiety with concomitant incorporation of a bromine atom at the C_5 position on the thiophene ring. The mixture of these brominated diastereomers was then subjected to dehydrobromination with 1,8-diazabicyclo[5.4.0]undecene-7 (DBU) in benzene at room temperature to provide dienone ester **78** in 67% yield over two steps

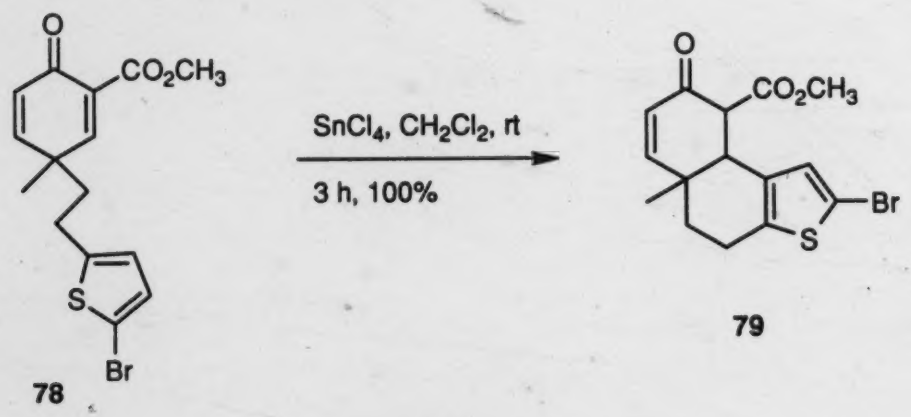


75 **78**

Scheme 51

after 4 hours (Scheme 51). Of particular structural diagnosis was the ir absorption at 1742 cm^{-1}, characteristic of ester carbonyl group, and another band absorbed at 1666 cm^{-1} exhibited the existence of the enone carbonyl functionality. In the ^1H nmr spectrum, compound **78** showed two signals at δ 6.81 and 6.43 with the same coupling constant (J = 3.5 Hz). This coupling pattern, in addition to the disappearance of one aromatic proton, suggested that a bromine atom was incorporated at the C_5 position of the thiophene ring. Also, compound **78** displayed a vinylic proton at δ 7.47 as a doublet (J = 3 Hz) belonging to H_3 which was substantially deshielded by both ketone and ester

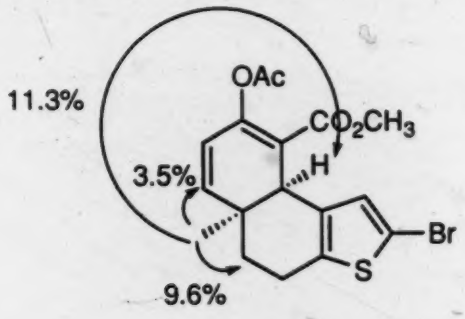
functionalities. Two other olefinic protons appeared at δ 6.75 (dd, J = 3 and 10 Hz) and 6.36 (d, J = 10 Hz), indicative of *cis*-disubstituted olefin. The methoxy and methyl singlets were shown at δ 3.85 and 1.34, respectively. In addition, the structure of this compound was confirmed by the ^{13}C APT nmr spectrum in which the ketone carbonyl signal was displayed at δ 181.3, whereas the ester carbonyl signal appeared at δ 164.9. In the high resolution mass spectrum, compound **78** displayed a molecular ion peak at m/z 355.9902 corresponding to the expected molecular formula $C_{15}H_{15}O_3S^{81}Br$.



Scheme 52

With enone ester **78** in hand, we examined its cyclization mode under Lewis acid catalysis. . When compound **78** was treated with stannic chloride in dichloromethane at room temperature for 3 hours, a quantitative yield of tricyclic product **79** was obtained (Scheme 52). We could notice that in comparision to that of compound **72**, the cyclization of compound **78** required a higher temperature and a longer period of time. The rationale behind this observation was the deactivation power the bromine atom had on the thiophene ring due to

its electron-withdrawing nature. However, the cyclization still proceeded with a high degree of efficiency. Keto ester **79** was shown to exist mostly in its enol form as indicated by ^1H nmr spectrum in which the signal of the hydroxyl proton was displayed at δ 12.01 as a sharp singlet. Furthermore, its high resolution mass spectrum depicted a molecular ion peak at m/z 355.9868, in agreement with the molecular formula $C_{15}H_{15}O_3S^{81}Br$. The confirmation of its structure was also achieved by acetylation giving rise to the corresponding enol



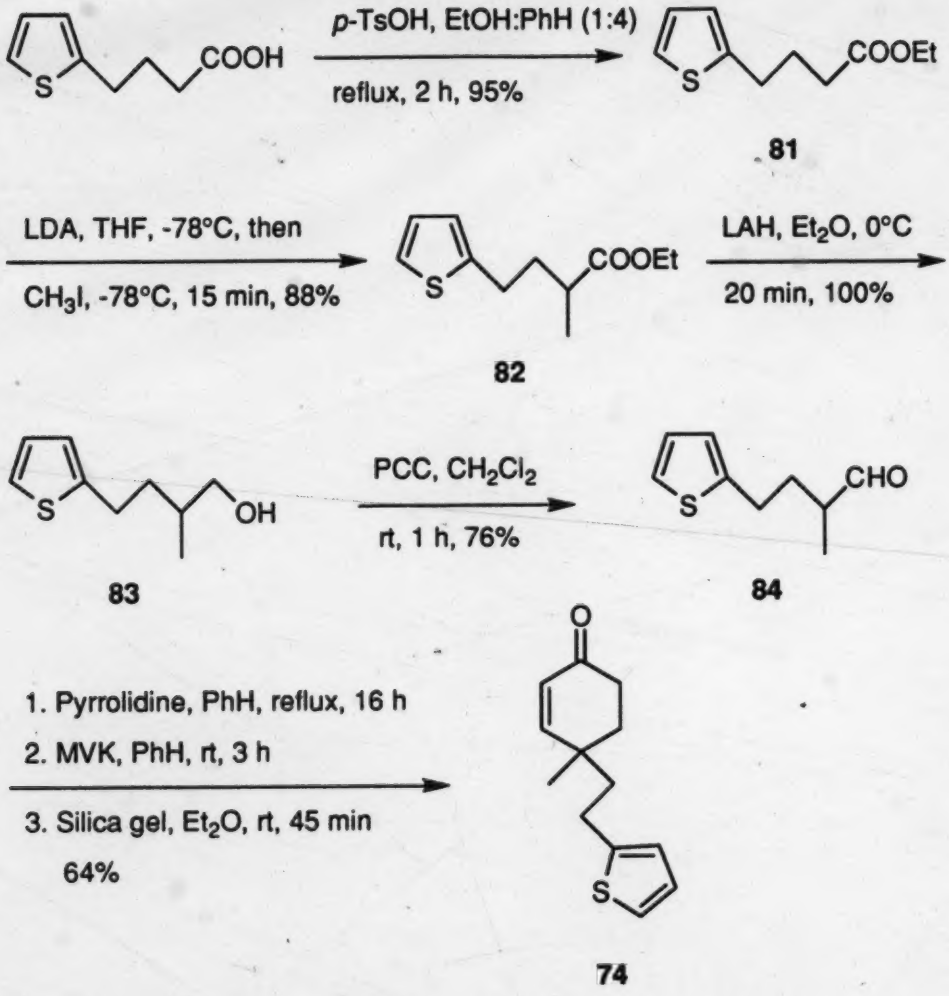
80

Figure 8

acetate **80**, structure of which was assigned by spectroscopic means. The ir spectrum displayed two carbonyl absorption bands at 1766 (enol acetate) and 1710 cm^{-1} (ester). The high resolution mass spectrum showed a molecular ion peak at m/z 397.9996, consonant with the molecular formula $C_{17}H_{17}O_4SBr$, which was also supported by elemental analysis. The ^{13}C APT nmr spectrum of compound **80** displayed two carbonyl signals at δ 168.3 (CH_3CO_2-) and 166.4 (CO_2CH_3). In the ^1H nmr spectrum, the aromatic proton was seen at δ 6.61 as a singlet, whereas the two vinylic protons appeared at δ 6.03 (dd, J = 1.5 and 10 Hz) and 5.69 (d, J = 10 Hz), characteristic of a *cis*-disubstituted olefin. In

addition, three methyl singlets were observed at δ 3.84, 2.24 and 1.22, whereas the ring junction proton was found in the low field region as a doublet (J = 1.5 Hz) at δ 3.73, due to the deshielding effects exerted by both the thiophene ring and the conjugated double bond. To determine the stereochemistry of the cyclization product **79**, NOE experiment was carried out on its corresponding enol acetate **80** (Figure 8). Thus, irradiation of the angular methyl group at δ 1.22 resulted in enhancements of ring junction proton (11.3%), nearby vinylic proton (3.5%) and the adjacent methylene protons (9.6%).

An alternative synthetic route to the synthesis of compound **74** was also examined (Scheme 53). In this approach, Robinson annulation reaction[55] was explored as a means to construct the 4,4-disubstituted six-membered ring. In this regard, the commercially available 4-(2-thienyl)butyric acid was subjected to esterification with *para*-toluenesulfonic acid in ethanol and benzene under reflux for 2 hours to provide ester **81** in 95% yield. The structure of compound **81** was assigned based on spectroscopic methods. In the ir spectrum, an absorption band was found at 1733 cm^{-1}, indicating the presence of the ester moiety. Its high resolution mass spectrum depicted a molecular ion peak at m/z 198.0712, corresponding to the desired molecular formula $C_{10}H_{14}O_2S$ which was corroborated by the nmr spectral data. For further synthetic transformations, it was necessary to introduce the methyl group to the position alpha to the carbonyl group. Thus, ester **81** was methylated at low temperature using LDA as the base to give compound **82** in 88% yield. In the ^1H nmr spectrum, this compound displayed three aromatic protons at δ 7.11 (dd, J = 1 and 5 Hz), 6.91 (dd, J = 3.5 and 5 Hz) and 6.79 (dd, J = 1 and 3.5 Hz). The presence of the ethyl ester moiety was evidenced by a quartet at δ 4.12 (J = 7



Scheme 53

Hz) and a triplet at δ 1.26 (J = 7 Hz), whereas the methyl group alpha to the carbonyl functionality was shown at δ 1.18 (d, J = 7 Hz). Furthermore, an absorption band was observed at 1732 cm^{-1} in the ir spectrum, indicative of ester moiety which was also supported by a signal at δ 176.3 in the ^{13}C APT nmr spectrum. In addition, compound **82** displayed a molecular ion peak at m/z

212.0869 in its high resolution mass spectrum. This along with the elemental analysis confirmed the desired formula $C_{11}H_{16}O_2S$.

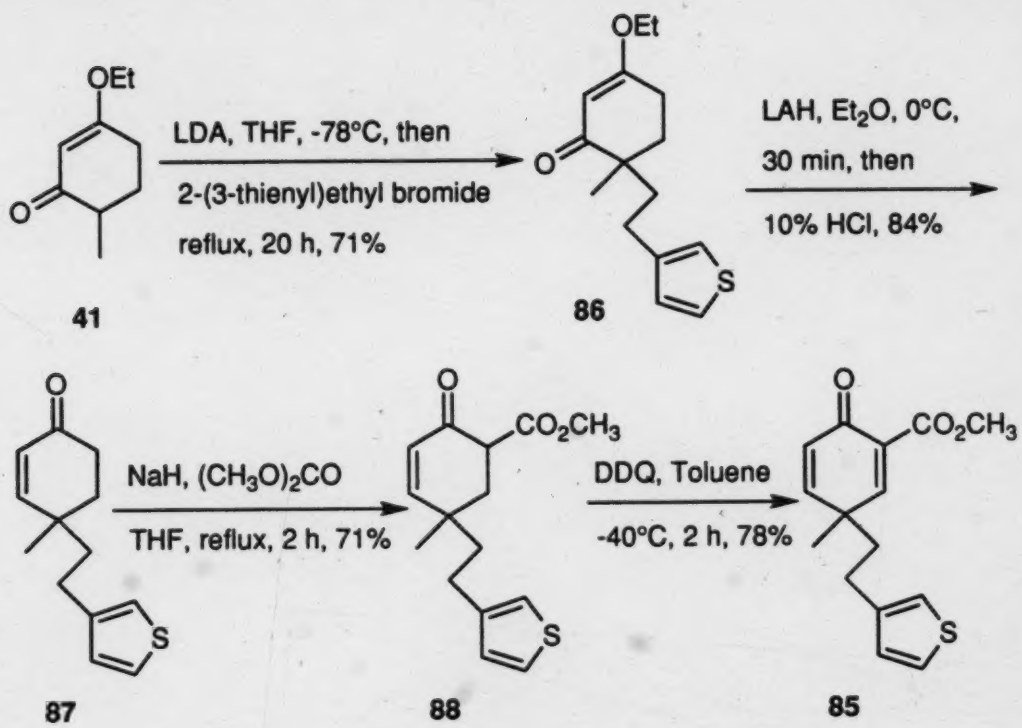
Compound **82** was reduced with lithium aluminum hydride in ether at 0°C to give a quantitative yield of alcohol **83** after 20 minuites. which displayed a broad absorption band at 3346 cm^{-1} in the ir spectrum, characteristic of a hydroxyl moiety. In the ^1H nmr spectrum, compound **83** showed three signals at δ 7.11 (dd, J = 1 and 5 Hz), 6.91 (dd, J = 3.5 and 5 Hz) and 6.80 (dd, J = 1 and 3.5 Hz) for the aromatic protons, whereas the hydroxyl proton and the methyl group appeared at δ 1.40 (d, J = 6 Hz) and 0.98 (d, J = 7 Hz), respectively. In addition, its high resolution mass spectrum displayed a molecular ion peak at m/z 170.0766 which was consistent with the molecular formula $C_9H_{14}OS$. Toward the synthesis of **74**, alcohol **83** was converted to its corresponding aldehyde **84** in 76% yield after 1 hour at room temperature when it was treated with pyridinium chlorochromate (PCC) in dichloromethane. The structure of compound **84** was established spectroscopically. The ir spectrum showed an absorption band at 1723 cm^{-1}, indicating the presence of the carbonyl group of the aldehydic functionality. The existence of the aldehyde moiety was also supported by the signals at δ 9.63 (d, J = 2 Hz) and 204.4 in the ^1H and ^{13}C APT nmr spectra, respectively. Furthermore, the molecular ion peak of aldehyde **84** was found at m/z 168.0607, in agreement with the molecular formula $C_9H_{12}OS$.

With compound **84** in hand, the elaboration to **74** could be accomplished in three manipulations. First, aldehyle **84** was allowed to react with pyrrolidine in benzene under reflux for 16 hours to generate the enamine derivative.

However, the formation of the enamine could not be dectected by thin layer chromatography (TLC) because it was readily hydrolyzed on silica gel. Thus, after the removal of pyrrolidine and benzene, the crude product was carried on with the second step by condensing with methyl vinyl ketone (MVK) in benzene at room temperature. After 3 hours, the crude condensation product was treated with silica gel in ether at room temperature for 45 minuites to give the desired enone **74** in 64% yield over three steps.

As a consequence, the results described above illustrated that the cross conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclization, which occurred readily leading to the formation of thiophene 3,2-fused tricyclic compounds. It was noteworthy that even with a poor nucleophilic thiophene due to the presence of the electron-withdrawing bromine atom, the cyclization still proceeded with a high degree of efficiency although the cyclization was comparably slower. These inspiring results led us to explore the preparation of thiophene 2,3-fused tricyclic compound. Thus, dienone ester **85**, visualized as the covetous precursor for the cyclization, was prepared from enone ester **41** according to Scheme 54.

Analogously, alkylation of **41** with LDA and 2-(3-thienyl)ethyl bromide afforded compound **86** in 71% yield, which displayed a carbonyl absorption at 1649 cm^{-1} in its ir spectrum. In the ^{1}H nmr spectrum, the vinylic proton appeared at δ 5.27 as a singlet. The attachment of the thienyl side chain was obvious from the signals of the three aromatic protons at δ 7.23 and 6.94 (2 protons), and the methyl singlet at δ 1.14. In addition to ^{13}C APT nmr spectrum, its molecular formula was confirmed as $C_{15}H_{20}O_2S$ by both the elemental analysis and the

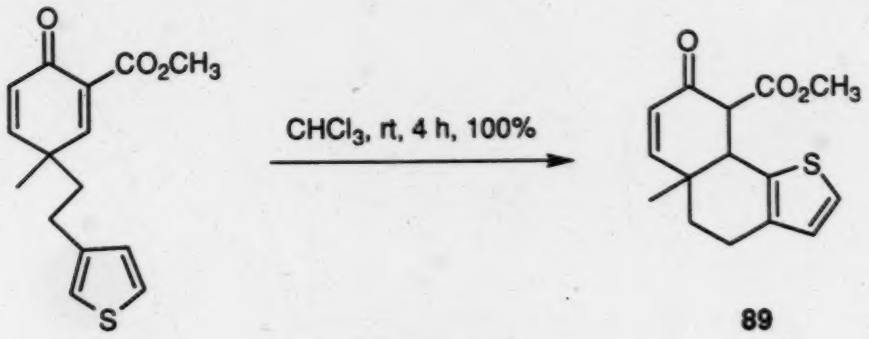


Scheme 54

high resolution mass spectrum. Reduction of **86** with lithium aluminum hydride in ether at 0°C, followed by acid hydrolysis with 10% HCl gave rise to enone **87** (84% yield). The structure of enone **87** was assigned by spectroscopic means. In the ir spectrum, a carbonyl absorption was observed at 1679 cm^{-1}, signifying the presence of enone moiety. In the ^1H nmr spectrum, the two vinylic protons appeared at δ 6.71 and 5.91, each as a doublet with a coupling constant of 10 Hz, presenting a *cis*-disubstituted olefin. An aromatic proton was observed at δ 7.26 as a doublet of doublet (J = 3 and 5 Hz) and the other two aromatic protons were found to overlap at δ 6.94. Also, the methyl group was located at δ 1.23 as a sharp singlet. The high resolution mass spectrum displayed a

molecular ion peak at m/z 220.0909, corresponding to the required formula $C_{13}H_{16}OS$ which was corroborated by the elemental analysis. For further synthetic operation, compound **87** was subjected to carbomethoxylation with dimethyl carbonate and sodium hydride in refluxing tetrahydrofuran for 4 hours. The desired product **88** thus formed in 71% yield was shown to exist as a mixture of two keto forms (1:1, 70%) and an enol form (30%). The ir spectrum confirmed the existence of ketone and ester carbonyl groups, showing absorption bands at 1743 (ester) and 1680 cm^{-1} (ketone). In the ^1H nmr spectrum, the hydroxyl proton of the enol form appeared at δ 11.99, whereas the alpha protons of the keto ester epimers displayed signals at δ 3.62 and 3.57. The methyl protons of the ester moiety of keto epimers were shown at δ 3.78 as a singlet, whereas the methyl protons of the ester moiety of the enol tautomer were found at δ 3.81, also as a singlet. Moreover, in its high resolution mass spectrum, the molecular formula $C_{15}H_{18}O_3S$ was assured by the molecular ion peak at m/z 278.0969. The elemental analysis was also in agreement with the molecular composition. Oxidation of **88** with DDQ in toluene at -40°C afforded enone ester **85** in 78% yield. The structural outcome of this reaction was readily proven by spectroscopic methods. In the ir spectrum, two carbonyl absorption bands were displayed at 1741 (ester) and 1664 (ketone) cm^{-1}. In the ^1H nmr spectrum, compound **85** displayed the vinylic proton at δ 7.50 as a doublet (J = 3 Hz) belonging to H_3 which was deshielded by both ketone and ester functional groups. Two other olefinic protons appeared at δ 6.77 (dd, J = 3 and 10 Hz) and 6.35 (d, J = 10 Hz), characteristic of *cis*-disubstituted olefin. Also, the thiophene protons were observed at δ 7.24 (dd, J = 3 and 5 Hz), 6.89 (dd, J = 1 and 3 Hz) and 6.86 (dd, J = 1 and 5 Hz). The methoxy and methyl singlets were shown at δ 3.85 and

1.36, respectively. In addition, its high resolution mass spectrum revealed a molecular ion peak at m/z 276.0795, corresponding to the expected formula $C_{15}H_{16}O_3S$.



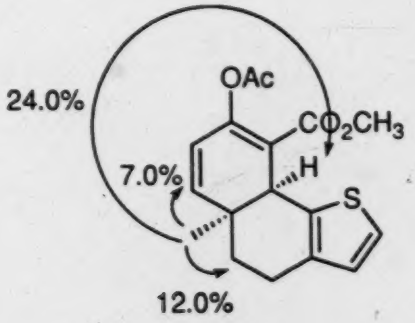
85 89

Scheme 55

Interestingly, dienone ester **85** was found to be so reactive that it cyclized by itself upon leaving in the fridge for a few days. Moreover, it underwent cyclization when it was dissolved in deuterated chloroform for ^1H nmr experiment. Ideally, the alpha position was the most electron rich carbon center of the thiophene ring and thus would be the most nucleophilic site of all. As expected, the cyclization of the dienone ester **85** was observed to be very facile when it was stirred in chloroform solution at room temperature for 4 hours to give a quantitative yield of the tricyclic thiophene derivative **89** (Scheme 55). Apparently, traces of hydrochloric acid present in chloroform solution facilitated the cyclization process in this particular case. Compound **89** was obtained mostly in its enol form as indicated by ^1H nmr spectrum in which the hydroxyl signal of the enol tautomer appeared at δ 12.06 as a broad singlet. The two aromatic protons were displayed at δ 7.07 (dd, J = 1 and 5 Hz) and 6.68 (d, J =

5 Hz), whereas the ring junction proton was shown at δ 3.83 as a broad doublet (J = 1 Hz). Its ir spectrum revealed the presence of an ester at 1743 cm^{-1}, an enone carbonyl at 1679 cm^{-1} as well as an enol ester at 1657 cm^{-1}. The molecular ion peak in accord with the molecular formula of $C_{15}H_{16}O_3S$ was found at m/z 276.0824 in the high resolution mass spectrum which was in agreement with the elemental analysis. From the previous experiences, we could predict that the above cyclization of **85** occurred to produce a *cis* fusion. However, evidence must be provided and thus the ring junction stereochemistry of compound **89** was established by its conversion to the corresponding enol acetate **90**, of which the regio- and stereochemistry were assigned (Figure 9).

In the ir spectrum, enol acetate **90** displayed two carbonyl absorption bands at 1766 cm^{-1} (enol acetate) and 1712 cm^{-1} (α,β-unsaturated ester), which were also evident from the signals at δ 168.3 and 165.8 in the ^{13}C APT nmr spectrum, respectively. Further confirmation of the structure was derived from



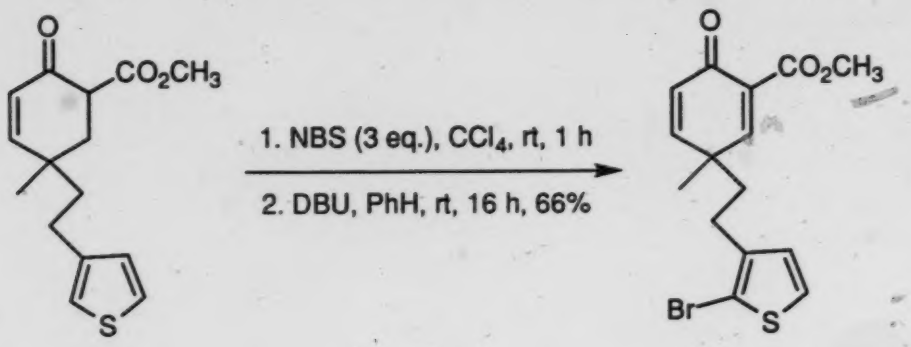
90

Figure 9

the ^1H nmr spectrum in which a doublet of doublet (J = 1.5 and 10 Hz) at δ 6.07 and a doublet (J = 10 Hz) at δ 5.69 were attributed to the vinylic protons. The two aromatic protons appeared at δ 7.09 (dd, J = 1 and 5 Hz) and 6.69 (d, J = 5 Hz), whereas the ring junction proton was observed as a doublet (J = 1 Hz) at δ 3.99, and the angular methyl was found at δ 1.26 as a sharp singlet. In the high resolution mass spectrum, the molecular ion peak was found at m/z 318.0927 which was consistent with the molecular formula $C_{17}H_{18}O_4S$. As shown in Figure 9, the *cis* ring junction of cyclization product **89** was readily established by the NOE experiment performed on compound **90**. Thus, irradiation of the angular methyl group at δ 1.26 provided enhancement of ring junction proton (24.0%), the adjacent vinylic proton (7.0%) and the nearby methylene protons (12.0%).

Again, the cross-conjugated β-keto ester system was demonstrated as an excellent promoter for the polyene cyclization. Specifically in this case, it was proven to be a very powerful tool for the preparation of thiophene 3,2-fused tricyclic compound. This encouraging result led us to examine the synthesis of thiophene 3,4-fused tricyles. In principle, if we could manage to block the C_2 position of the thiophene ring in compound **85**, we could somewhat force the resulting molecule to cyclize at the C_4 center of the thiophene ring. From this line of reasoning, bromine atom was deemed as a good candidate, as it was previously noticed that the thiophene ring could readily undergo electrophilic aromatic substitution when it was treated with NBS; especially in this case, it would be brominated at C_2 center.

As expected, when keto ester **88** was subjected to the bromination and dehydrobromination sequence, dienone ester **91** was obtained in 66% yield over two steps (Scheme 56). In this particular case, compound **91** displayed



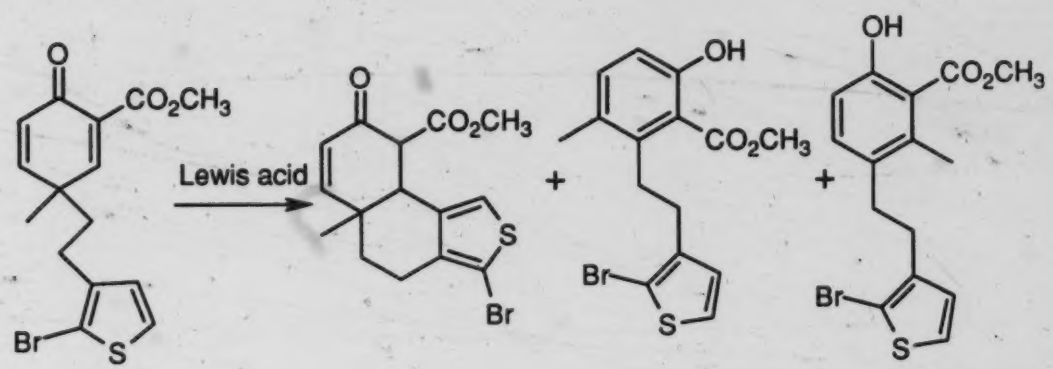
88 **91**

Scheme 56

the carbomethoxy carbonyl at δ 165.6 and the ketone carbonyl at δ 180.6 in the ^{13}C APT nmr spectrum which were corroborated by the absorption bands at 1741 (ester) and 1664 cm^{-1} (ketone) in the ir spectrum. In the ^{1}H nmr spectrum, three vinylic protons were observed at δ 7.05 (d, J = 3 Hz), 6.61 (d, J = 10 Hz) and 5.88 (dd, J = 3 and 10 Hz). Also, the splitting patterns of the protons on the heteroaromatic ring were both noticed as doublets with the same coupling constant (J = 5.5 Hz) at δ 6.61 and 6.22, suggesting the protons at C_4 and C_5 of the thiophene ring. In addition, the methoxy and methyl singlets were shown at δ 3.52 and 0.62, respectively. The presence of the bromine atom was firmly supported by mass spectral data which revealed the molecular ion peak at m/z 353.9974, corresponding to the molecular formula $C_{15}H_{15}O_3S^{79}Br$.

With the bromo compound **91** in hand, its cyclization was investigated, in which the particular Lewis acids such as zinc chloride, stannic chloride and aluminum chloride, were chosen. The results are summarized in Table 5.

Table 5. Reaction of compound **91** under Lewis acid catalysis



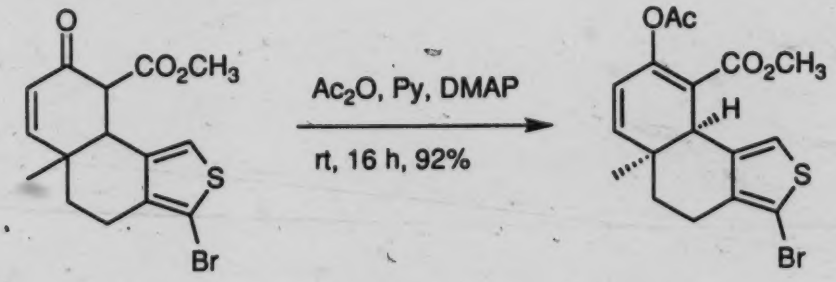
91 **92** **93** **94**

Condition	Time	92 (% yield)	93 (% yield)	94 (% yield)
$ZnCl_2$, Et_2O, rt	16 h	N.R.		
$SnCl_4$, CH_2Cl_2, rt	1 h	30	54	6
$AlCl_3$, Et_2O, 0°C	2 h	80	12	1

The cyclization of enone ester **91** was attempted using anhydrous zinc chloride in ether at room temperature for 16 hours. Unfortunately, no cyclization product was detected, and the starting material was recovered intact. Obviously, zinc chloride was not strong enough as a Lewis acid to facilitate the ring closure

process. On the other hand, when stannic chloride was used as a reagent and dichloromethane as a solvent, after 1 hour at room temperature, the reaction provided a mixture of the desired tricyclic product **92** and the aromatization products **93** and **94** in a ratio of 5:9:1, respectively. However, when stannic chloride was replaced by aluminum chloride, a remarkable enhancement of the reaction rate as well as selectivity was observed. The reaction occurred at 0°C and the tricyclic product **92** was produced in 80% yield along with a small amount of aromatization products after 2 hours.

Apparently, the presence of a bromine atom at C_2 of the thiophene ring in compound **91** decreased, to some extent, the reactivity of the thiophene ring and as a result brought about a competition between side chain migration process and cyclization. Compound **92** was obtained as an inseperable mixture of isomers due to the presence of the highly enolizable and epimerizable β-keto ester moiety. The regiochemistry and stereochemistry of this compound was assigned as follows. Treatment of compound **92** with acetic



92 **95**

Scheme 57

anhydride in pyridine gave rise to the corresponding enol acetate **95** (Scheme 57), whose structure was verified by spectroscopic methods, especially nmr spectroscopy with the assistance of NOE experiment.

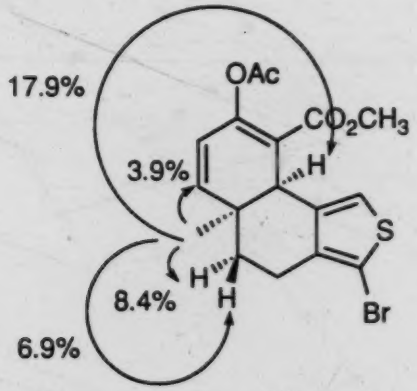
Table 6. ^{1}H nmr spectral data of compound **95**

Proton	**δ** (in ppm)	**Multiplicity** (J in Hz)
Ar**H**	6.87	d (J = 2)
CH=CHCOAc	6.07	dd (J = 2, 10)
CH=CHCOAc	5.69	d (J = 10)
OCH_3	3.84	s
ring junction **H**	3.72	br. s
$ArCH_2$	2.73	ddd (J = 2, 5.5, 18)
$ArCH_2$	2.44	ddd (J = 5.5, 13.5, 18)
CH_3CO_2	2.24	s
CH_2	2.00	ddd (J = 2, 5.5, 13.5)
CH_2	1.79	ddd (J = 5.5, 13.5, 13.5)
CH_3	1.23	s

The ir spectrum of acetate **95** displayed two carbonyl absorptions at 1766 (CH_3COO) and 1710 cm^{-1} (CO_2CH_3). The high resolution mass spectrum showed a molecular ion peak at m/z 396.0039 in agreement with the required

molecular formula $C_{17}H_{17}O_4S^{79}Br$. In the ^1H nmr spectrum, the heteroaromatic proton was observed as a doublet (J = 2 Hz) at δ 6.87, whereas the ring junction proton appeared at δ 3.72 as a broad singlet. The complete set of ^1H nmr data of compound **95** is shown in Table 6.

The *cis* ring junction of compound **95** was determined with the aid of NOE experiment. Thus, irradiation of the angular methyl singlet at δ 1.23 resulted in 17.9% enhancement on the ring junction proton at δ 3.72 (Figure 10), indicating the depicted stereochemistry of enol acetate **95**.

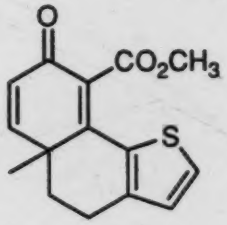


95

Figure 10

As illustrated above, the polyene cyclization induced by the cross conjugated β-keto ester system presents itself as an excellent synthetic method for the six-membered ring formation of all three possible isomeric thiophene fused polycyclic compounds (2,3-, 3,2- and 3,4-fused). The cyclization is rapid under mild conditions, highly regio- and stereoselective, and the products which contain a high degree of functionalization are formed in uniformly high yield.

This approach can be extended to the preparation of a variety of polycyclic thiophene derivatives for pharmacological evaluation by suitable selection of the reactants and by modification of the existing functionalities in the products. For example, oxidation of tricyclic thiophene **89** with DDQ and a catalytic amount of acetic acid in THF for 4 days at room temperature gave the corresponding dienone thiophene **96** in 98% yield.

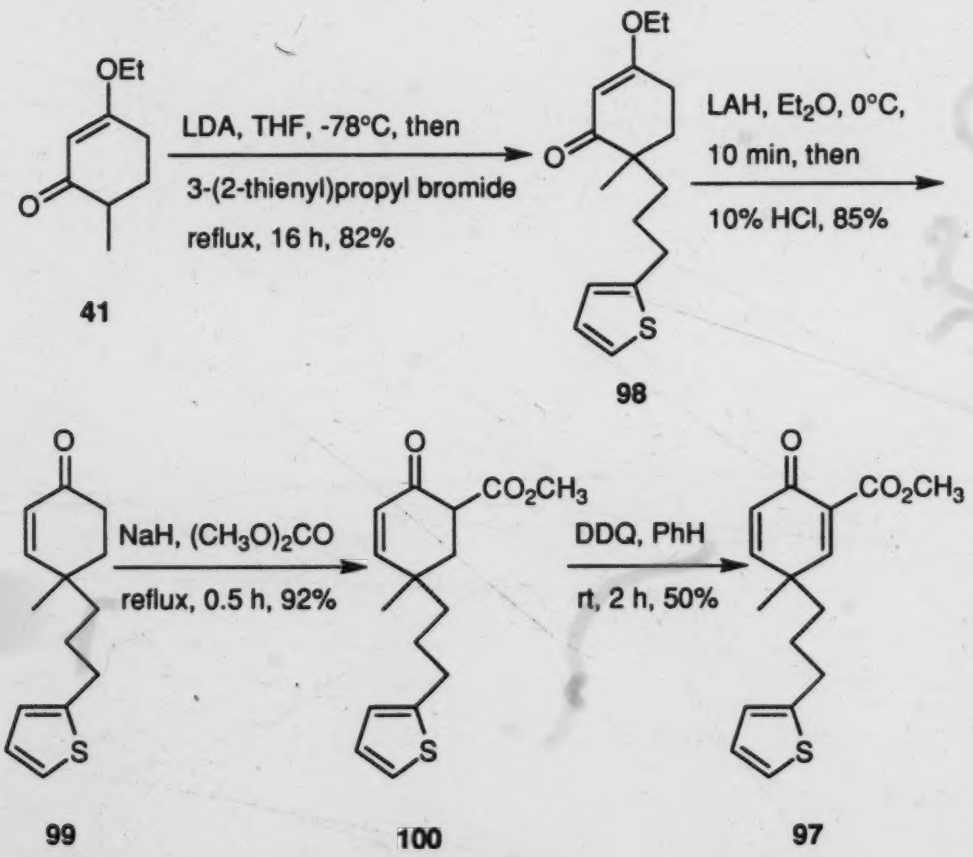


96

At this point, we decide to extend the C_4 thiophene-containing side chain to a three-carbon unit. The required enone ester **97** could be synthesized from enone **41** *via* a sequence similar to those used previously for the preparation of the analogous compounds (Scheme 58).

Alkylation of **41** with LDA and 3-(2-thienyl)propyl bromide afforded an 82% yield of compound **98**, which displayed a carbonyl absorption at 1652 cm^{-1} in its ir spectrum. In the ^1H nmr spectrum, the vinylic proton of the enone system appeared at δ 5.24 as a sharp singlet. Three aromatic protons appeared at δ 7.09 (dd, J = 1 and 5 Hz), 6.90 (dd, J = 3.5 and 5 Hz) and 6.77 (dd, J = 1 and 3.5 Hz). The ethoxy group was inferred by the signals at δ 3.88 (q, J = 7 Hz) and 1.35 (t, J = 7 Hz). The ^{13}C APT nmr spectrum showed a carbonyl carbon at δ

204.0. The high resolution mass spectrum displayed a molecular ion peak at m/z 278.1342, corresponding to the required formula $C_{16}H_{22}O_2S$. Compound **98** was subjected to reduction with lithium aluminum hydride, followed immediately by hydrolysis with 10% HCl to give enone **99** in 85% yield over two



Scheme 58

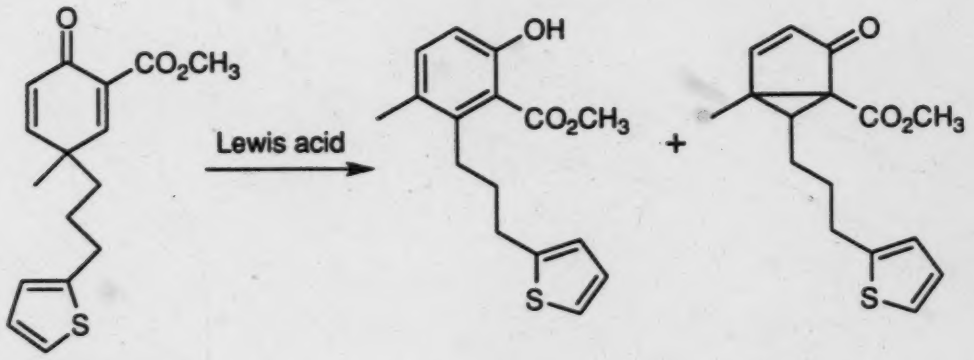
operational steps. The ir spectrum of this compound showed a carbonyl absorption at 1681 cm^{-1}, characteristic of an enone. In the ^1H nmr spectrum, two vinylic protons of the enone system appeared at δ 6.66 and 5.87 with the same coupling constant (J = 10 Hz), indicative of a *cis*-disubstituted olefin. The

intactness of the thiophene ring was evidenced by the signals at δ 7.12 (dd, J = 1 and 5 Hz), 6.92 (dd, J = 3.5 and 5 Hz) and 6.79 (dd, J = 1 and 3.5 Hz), whereas the presence of the methyl group was shown by the singlet at δ 1.14. The ^{13}C APT nmr spectrum displayed the carbonyl carbon at δ 199.5. In the high resolution mass spectrum, the molecular ion peak was shown at m/z 234.1082, in agreement with the required formula $C_{14}H_{18}OS$.

To continue the synthesis with compound **99**, carbomethoxylation of **99** using dimethyl carbonate and sodium hydride gave keto ester **100** (74% yield) as a mixture of two keto and an enol forms in a ratio of 3:4:4, respectively, as indicated by the ^{1}H nmr spectrum in which the enol proton was observed as a singlet at δ 11.87. In the ir spectrum, keto ester **100** displayed two carbonyl absorption bands at 1743 (ester) and 1679 (ketone) cm^{-1}. In addition, its molecular formula was confirmed as $C_{16}H_{20}O_3S$ by the high resolution mass spectrum displaying a molecular ion peak at m/z 292.1134. Oxidation of compound **100** with DDQ afforded, in 50% yield, the desired enone ester **97** which showed carbonyl absorptions at 1742 cm^{-1} for the ester moiety and 1667 cm^{-1} for the ketone functionality in its ir spectrum. In the ^{1}H nmr spectrum, a doublet at δ 6.99 (J = 3 Hz) was observed for the C_3 proton which was simultaneously deshielded by the ketone and ester functional groups. The vinylic protons of the enone system appeared at δ 6.12 (d, J = 10 Hz) and 5.87 (dd, J = 3 and 10 Hz), whereas the three aromatic protons were shown at δ 6.81 (dd, J = 1 and 5 Hz), 6.72 (dd, J = 3.5 and 5 Hz) and 6.53 (dd, J = 1 and 3.5 Hz). Also, the methoxy and methyl singlets were found at δ 3.85 and 0.55, respectively. For further structural confirmation, the ^{13}C APT nmr spectrum showed two carbonyl carbons at δ 180.7 and 165.7, and eight sp^2 cabons

between δ 158.4 and 123.4. In the high resolution mass spectrum, the molecular ion peak was found at m/z 290.0980, in consonance with the required formula $C_{16}H_{18}O_3S$ which was further supported by the elemental analysis.

Table 7. Reaction of compound **97** under Lewis acid catalysis



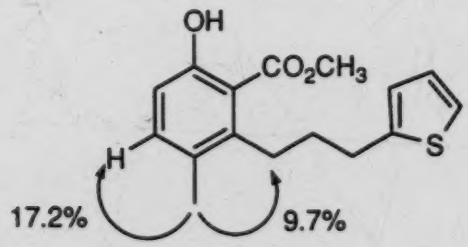
97 **101** **102**

Conditions	Time	**101** (% yield)	**102** (% yield)
$SnCl_4$ (1.5 eq.), CH_2Cl_2, 0°C	1 h	35	32
$AlCl_3$ (1.5 eq.), Et_2O, 0°C	1 h	64	0

With enone ester **97** in hand, we were able to examine its cyclization under Lewis acid catalysis. When enone ester **97** was treated with stannic chloride in dichloromethane at 0°C for 1 hour, a mixture of migration products **101** and **102** were produced in 67% yield (Table 7). Similarly, when stannic chloride was replaced with aluminum chloride and the reaction was carried out in ether

at 0°C, there was no cyclization product observed, but instead compound **101** was formed exclusively in 64% yield in this particular case.

The structure of these products were determined spectroscopically as follows. The high resolution mass spectrum of compound **101** showed a molecular ion peak at m/z 290.0973 corresponding to the formula $C_{16}H_{18}O_3S$. In its ir spectrum, the carbonyl of the ester moiety was observed at 1732 cm^{-1}, which was also supported by the signal at δ 171.9 in the ^{13}C APT nmr spectrum. In the ^1H nmr spectrum, a sharp singlet at δ 10.59 was easily recognized for the phenolic proton. Two doublets due to aromatic protons of the phenol ring appeared at δ 7.18 (d, J = 10 Hz) and 6.75 (d, J = 10 Hz). From the coupling pattern, it is clear that these aromatic protons have an *ortho* relationship. The methoxy and methyl groups appeared at δ 3.86 and 2.21, respectively, each as a singlet. The regiochemistry of compound **101** was further confirmed by NOE experiments. As shown in Figure 11, irradiation of the methyl signal at δ 2.21 resulted in enhancements of H_5 (17.2 %) and the methylene protons adjacent to the phenol ring (9.7%).



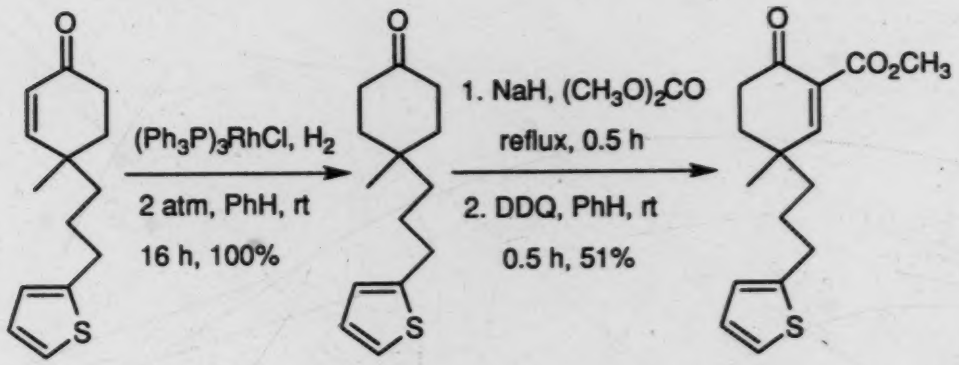
101

Figure 11

Compound **102** displayed two carbonyl absorption bands at 1739 (ester) and 1676 (enone) cm^{-1} in its ir spectrum, which were also indicated by the signals at δ 194.0 and 172.6 in the ^{13}C APT nmr spectrum. In the ^{1}H nmr spectrum, two vinylic protons of the enone system were observed at δ 6.66 (d, J = 10 Hz) and 6.25 (d, J = 10 Hz), characteristic of *cis*-disubstituted olefin. In addition, the presence of the thiophene ring was verified by the proton signals at δ 7.13 (dd, J = 1 and 5 Hz), 6.90 (dd, J = 3.5 and 5 Hz) and 6.81 (multiplets). The methyl protons of the ester moiety appeared at δ 3.69, while the quarternary methyl was shown at δ 1.23, each of which was a sharp singlet. Furthermore, compound **102** showed a molecular ion peak at m/z 290.0972 in its high resolution mass spectrum, in agreement with the molecular formula $C_{16}H_{18}O_3S$.

The formation of compound **101** and **102** could again be rationalized by invoking a 1,2-alkyl shift followed by either aromatization or cyclization. In this particular case, the preferential migration of the thiophene-containing side chain is in accord with the general observation that the more substituted alkyl group migrates in preference to the less substituted alkyl group.[56] Nevertheless, to suppress the migration process of the side chain, a possible solution would be to remove the disubstituted carbon-carbon double bond. Thus, the preparation of the required enone ester **103**, commenced with reduction of the conjugated carbon-carbon double bond of **99**, was carried out (Scheme 59). When enone **99** was subjected to catalytic hydrogenation with Wilkinson's catalyst under two atmospheres of hydrogen using benzene as the solvent at room temperature for about 16 hours, ketone **104** was obtained exclusively in quantitative yield. The ir spectrum of this compound displayed a

carbonyl absorption at 1716 cm^{-1}. In the ^1H nmr spectrum, three aromatic protons appeared at δ 7.02 (dd, J = 1 and 5 Hz), 6.83 (dd, J = 3.5 and 5 Hz) and 6.71 (dd, J = 1 and 3.5 Hz). A methyl singlet was found at δ 0.92. Moreover, its high resolution mass spectrum showed a molecular ion peak at m/z 236.1239, in consonance with the formula $C_{14}H_{20}OS$. To continue the synthesis of **103**, carbomethoxylation of ketone **104** with dimethyl carbonate and sodium hydride

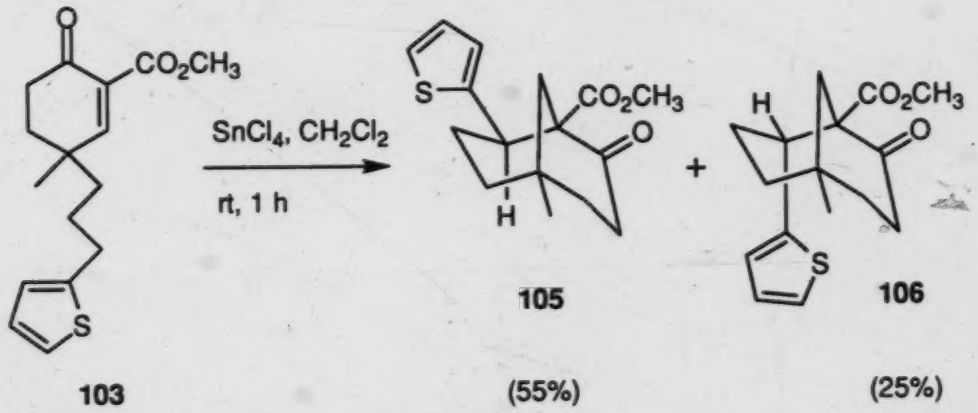


99 **104** **103**

Scheme 59

followed by DDQ oxidation afforded the desired enone ester **103** in 51% yield over two steps. Compound **103** showed carbonyl absorption bands at 1743 cm^{-1} for the ester and 1686 cm^{-1} for the ketone in its ir spectrum. In the ^1H nmr spectrum, a singlet at δ 7.35 was observed for the C_3 proton. Three aromatic protons appeared at δ 7.13 (dd, J = 1 and 5 Hz), 6.92 (dd, J = 3.5 and 5 Hz) and 6.79 (br. d, J = 3.5 Hz). The methoxy and methyl groups were shown at δ 3.79 and 1.19, respectively, each as a singlet. In its high resolution mass spectrum, the molecular ion peak was found at m/z 292.1131, in agreement with the required formula $C_{16}H_{20}O_3S$.

Interestingly, when compound **103** was treated with stannic chloride in dichloromethane at room temperature for 1 hour, a mixture of two diastereomers **105** and **106** was formed in 80% yield in a ratio of approximately 1:2, respectively (Scheme 60). The major product **105** showed, in the ir spectrum, two carbonyl absorptions at 1738 (ester) and 1710 (ketone) cm^{-1}. In the ^1H nmr spectrum, the signals at δ 7.11 (dd, J = 1 and 5 Hz), 6.88 (dd, J = 3.5 and 5 Hz) and 6.81 (dd, J = 1 and 3.5 Hz) are attributed to the protons on the thiophene ring. Also, the proton alpha to the thiophene ring was observed to undergo a



103 **105** (55%) **106** (25%)

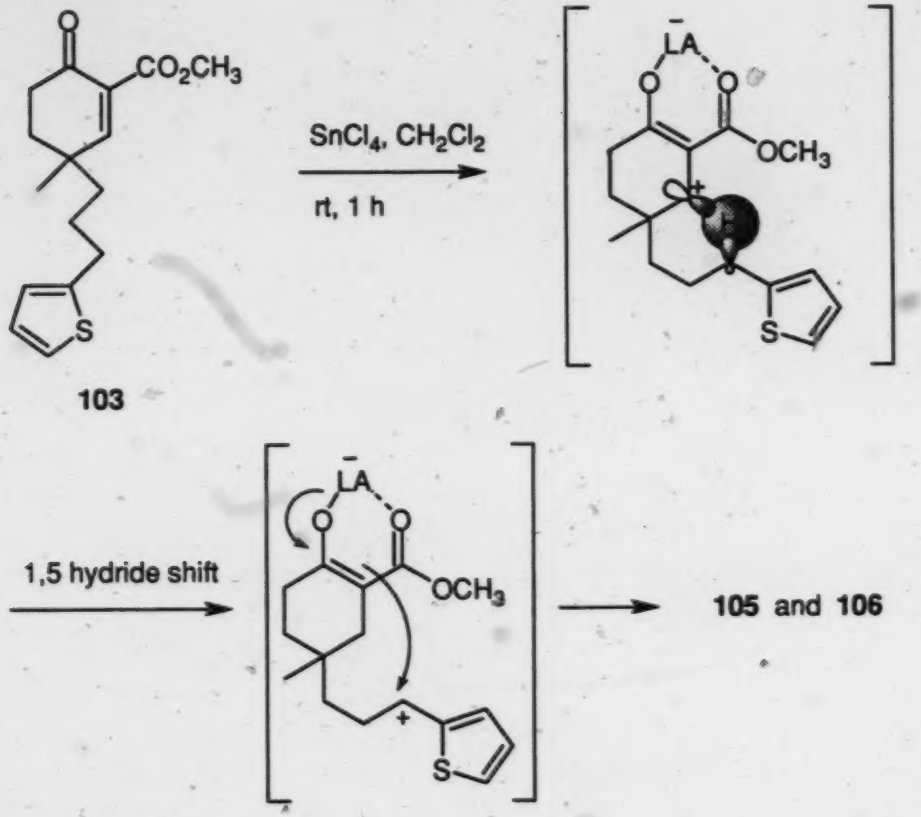
Scheme 60

down-field shift to δ 3.60 as a doublet of doublets (J = 5 and 13 Hz), due to the deshielding effect exerted by both thiophene ring and ester functional group. The presence of the methoxy group was indicated by the singlet at δ 3.61, while the angular methyl singlet was found at δ 1.02. In the ^{13}C APT nmr spectrum, compound **105** displayed a total of 16 signals, of which two carbonyl signals at δ 207.2 and 172.5 were indicative of the ketone and ester moieties. The molecular formula of this compound was confirmed as $C_{16}H_{20}O_3S$ by its high

resolution mass spectrum displaying a molecular ion peak at m/z 292.1137. The structure of the minor isomer **106** was also established spectroscopically. In the ir spectrum, two carbonyl bands were displayed at 1750 (ester) and 1714 (ketone) cm^{-1}. In the ^{1}H nmr spectrum of this particular compound, the proton alpha to the thiophene ring was found at δ 4.04 as a broad doublet (J = 4.5 Hz), while the methoxy and angular methyl singlets appeared at δ 3.52 and 1.10, respectively. In addition to the signals of the thiophene ring in the ^{13}C APT nmr spectrum, compound **106** showed two carbonyl signals at δ 209.6 and 169.8, characteristic of the ester and ketone moieties. The high resolution mass spectrum revealed the molecular ion peak at m/z 292.1129 in accordance with the molecular formula $C_{16}H_{20}O_3S$.

Literature studies on hydride shift indicated that, though rare, the hydride shifts of higher order than 1,3 occur if the migration origin and the migration teminus are close together, and the geometry of the system allows overlap of the orbitals of hydrogen and of the migration teminus. Frequently, these reactions proceed through a cyclic transition state in which a new C-H bond is formed simultaneously with the C-H cleavage. As well, hydride transfer is facilitated by high charge density at the carbon atom. As a consequence, it seems reasonable that the formation of the products **105** and **106** occurred *via* the rearrangement process outlined in Scheme 60. The initiation must occur *via* the coordination of stannic chloride to form a highly electron-deficient center at C3 which then overlapped with the orbital of the hydrogen alpha to the thiophene ring forming a six-membered ring transition state. In that case, this overlap was capable of transferring a hydride from the benzylic-typed position to the carbonium center leading to the formation of the more stable carbocation

107, due to the electron-rich properties of the thiophene ring. The subsequent cation-induced ring closure was followed to produce the observed products **105** and **106**.



103

107

Scheme 61

Although the preparation of tricyclic compound with a central seven-membered ring fused to a thiophene using stannic chloride provided an unsatisfactory result, the use of other Lewis acids could possibly bring about a desirable

conformation of the keto ester **103**, surmounting the energy barrier for an efficient cyclization. This idea is currently being investigated.

In conclusion, the results described in this chapter of the thesis illustrated that the cross conjugated β-keto ester system could serve as a highly effective promoter for cationic cyclization involving a thiophene ring, which occurred readily with regio- and stereoselectivity. In essence, this cyclization process allows for expeditious construction of highly functionalized polycyclic thiophene-containing compounds which can be interesting for pharmacological evaluation.

Experimental

General and materials

For general and materials used in Chapter 2, refer to Chapter 1 of this thesis.

General Procedure for Alkylation Using LDA

To a solution of diisopropylamine (3.18 mL, 19.44 mmol) in dry THF (10 mL) at 0°C under an argon atmosphere, was added *n*-BuLi (2.5 M in hexane, 7.78 mL, 19.44 mmol) slowly. The mixture was stirred at 0°C for 15 min and then cooled to -78°C with a dry ice-acetone bath. A solution of enone **41** (1.2 g, 6.48 mmol) in THF (3 mL) was added dropwise over a period of 10 min. The resulting mixture was stirred at -78°C for 1 h followed by the dropwise addition of alkyl bromide (4.95 g, 25.92 mmol) in THF (5 mL). The mixture was allowed to warm slowly to room temperature and then refluxed overnight. Saturated ammonium chloride was added and the mixture was extracted with ether (3 x 20 mL). The extracts were combined, washed with water and brine, and dried over magnesium sulfate. Filtration and concentration followed by flash column chromatography using diethyl ether/hexane (50:50) as an eluent gave rise to the pure alkylation product.

General Procedure for $LiAlH_4$ Reduction Followed by Acidic Hydrolysis

To a suspension of lithium aluminum hydride (43 mg, 1.13 mmol) in Et_2O (5 mL) at 0°C under an argon atmosphere, was added dropwise a solution of the alkylated enone (300 mg, 1.13 mmol) in anhydrous diethyl ether (5 mL). The resulting mixture was stirred at 0°C for 15 min. The reaction mixture was then hydrolyzed and the excess lithium aluminum hydride was destroyed by cautious addition, dropwise and with stirring, of water. The resulting mixture was stirred for another hour and then acidified with 10% HCl. The resulting solution was stirred for 4 h. After the hydrolysis was complete, the ether layer was separated, and the aqueous phase was extracted with three 10 mL portions of ether. The combined ether solutions were washed successively with saturated sodium bicarbonate (1 x 10 mL), water (1 x 10 mL) and brine (1 x 10 mL). After being dried over magnesium sulfate, the solution was filtered and concentrated to give the crude product, which was subjected to flash chromatography using ethyl acetate/hexane (5:95) as an eluent to give the enone.

General Procedure for Carbomethoxylation

To a stirred suspension of sodium hydride (49 mg, 2.03 mmol) in dry THF (5 mL) at room temperature under an argon atmosphere, was added a solution of enone (149 mg, 0.68 mmol) in THF (3 mL), followed by dry dimethyl carbonate (1.14 mL, 13.52 mmol). The reaction mixture was refluxed for 2 h and then cooled to room temperature. A solution of 10% acetic acid (10 mL) was added cautiously to the mixture. The resulting aqueous solution was extracted with diethyl ether (3 x 10 mL), and the combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure, and the crude product was purified by flash

chromatography (ethyl acetate/hexane, 5:95) on silica gel to afford the keto ester.

General Procedure for DDQ Oxidation

To a solution of keto ester (40 mg, 0.14 mmol) in dry benzene (2 mL) at room temperature under an argon atmosphere, was added DDQ (65 mg, 0.28 mmol). The mixture was stirred for 2 h at room temperature and the precipitate was removed by filtration. The filtrate was concentrated, and the crude product was subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give the enone ester.

General Procedure for Polyene Cyclization

A. Using $SnCl_4$ as Lewis Acid

A solution of enone ester (38 mg, 0.14 mmol) in dry dichloromethane (3 mL) was cooled to -78°C under an argon atmosphere with a dry ice-acetone bath. Stannic chloride (0.03 mL, 0.21 mmol) was added slowly. After being stirred for 15 min under these conditions, the starting material was completely consumed. The reaction mixture was quenched with saturated ammonium chloride, followed by water, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic solutions were washed with water, dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography (ethyl acetate/hexane, 5:95 as eluent) to give the cyclization product(s).

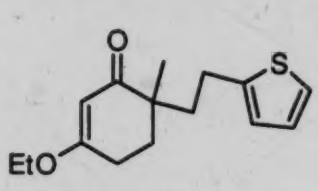
B. Using $AlCl_3$ as Lewis Acid

To a stirred suspension of anhydrous aluminun chloride (27 mg, 0.20 mmol) in dry diethyl ether (5 mL) at 0°C under an argon atmosphere, was added a solution of enone ester (24 mg, 0.07 mmol) in diethyl ether (1 mL). The reaction mixture was stirred at 0°C for 2 h and then quenched with ammonium chloride solution, followed by water. The aqueous solution was extracted with diethyl ether (3 x 5 mL). The organic solution was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (3:97) as an eluent to afford the cyclization product.

General Procedure for Acetylation of β-Keto Ester

To a solution of keto ester (28 mg, 0.10 mmol), in pyridine (3 mL) at room temperature under an argon atmosphere, was added acetic anhydride (1 mL) and DMAP (cat.). The reaction mixture was stirred overnight, and pyridine was removed under reduced pressure. Water was added and the resulting mixture was extracted with diethyl ether (3 x 10 mL). The ether extracts were washed with 10% hydrochloric acid and brine, dried over magnesium sulfate, filtered and concentrated. Flash chromatography of the residue using ethyl acetate/hexane (20:80) as an eluent gave the enol acetate.

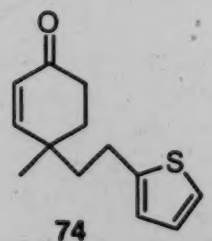
3-Ethoxy-6-methyl-6-[2-(2-thienyl)ethyl]-2-cyclohexenone (73)



73

Alkylation of enone **41** (1.0 g, 6.48 mmol) with LDA (19.44 mmol) and 2-(2-thienyl)ethyl bromide (4.28 g, 22.40 mmol) under reflux for 18 h gave compound **73** (0.95 g, 78% yield based on consumed starting material) along with a 40% recovery of starting material. Compound **73**: ir (CH_2Cl_2 cast) 2980, 1651 (C=O, enone), 1609 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.91 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.90 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.79 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 5.25 (1H, s, C=C**H**CO), 3.89 (2H, q, J = 7 Hz, CH_3CH_2O), 2.79 (2H, ddd, J = 4, 5, 10.5 Hz, CH_2), 2.45 (2H, ddd, J = 4, 7.5, 7.5 Hz, CH_2), 1.91 (4H, complex), 1.36 (3H, t, J = 7 Hz, CH_3CH_2O), 1.14 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 203.4 (p), 175.7 (p), 145.5 (p), 126.7 (a), 123.9 (a), 122.9 (a), 101.4 (a), 64.2 (p), 43.4 (p), 39.1 (p), 32.5 (p), 26.1 (p), 24.8 (p), 22.3 (a), 14.2 (a); hrms M^+: 264.1188 (calcd. for $C_{15}H_{20}O_2S$: 264.1184). Anal. calcd. for $C_{15}H_{20}O_2S$: C 68.15, H 7.63, S 12.13; found: C 67.97, H 7.60, S 12.11.

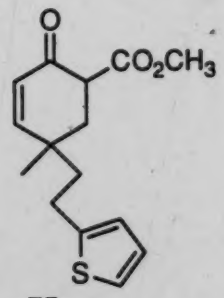
4-Methyl-4-[2-(2-thienyl)ethyl)]-2-cyclohexenone (74)



74

Compound **73** (300 mg, 1.13 mmol) was subjected to reduction using lithium aluminum hydride (43 mg, 1.13 mmol). This was followed by acid hydrolysis to afford enone **74** (240 mg, 96%): ir (CH_2Cl_2 cast) 2957, 1680 (C=O, enone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.12 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.92 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.80 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 6.71 (1H, d, J = 10 Hz, C**H**=CHCO), 5.91 (1H, d, J = 10 Hz, CH=C**H**CO), 2.87 (2H, complex), 2.49 (2H, complex), 2.04 (1H, ddd, J = 6, 8.5, 14 Hz, CH_2), 1.85 (3H, complex), 1.22 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.3 (p), 158.2 (a), 144.8 (p), 127.9 (a), 126.9 (a), 124.1 (a), 123.2 (a), 43.0 (p), 35.8 (p), 34.1 (p), 33.5 (p), 24.9 (p), 24.8 (a); hrms M^+: 220.0920 (calcd. for $C_{13}H_{16}OS$: 220.0922). Anal. calcd. for $C_{13}H_{16}OS$: C 70.88, H 7.33, S 14.53; found: C 70.62, H 7.58, S 14.40.

6-Carbomethoxy-4-methyl-4-[2-(2-thienyl)ethyl]-2-cyclohexenone (75)

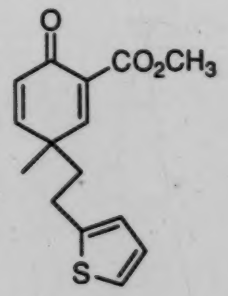


75

Carbomethoxylation of **74** (149 mg, 0.68 mmol) with dimethyl carbonate (2 mL) and sodium hydride (49 mg, 2.04 mmol) in THF (5 mL) for 4 h under reflux gave keto ester **75** (133 mg, 71%): ir (CH_2Cl_2 cast) 2952, 1743 (C=O, ester), 1681 (C=O, ketone), 1624 (C=O, enol ester), 1588 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300

MHz) a mixture of three isomers (two epimers and an enol) in a ratio of 1:1:1, δ: 11.89 (0.3H, s, OH), 7.12 (1H, complex, ArH), 6.94 (0.35H, d, J = 3.5 Hz, ArH, keto), 6.92 (0.35H, d, J = 3.5 Hz, ArH, keto), 6.90 (0.3H, d, J = 3.5 Hz, ArH, enol), 6.80 (1H, complex, ArH), 6.74 (0.35H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.72 (0.35H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.08 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 5.97 (0.7H, d, J = 10 Hz, CH=CHCO, keto), 5.93 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 3.78 (3H, s, OCH_3), 3.62 (0.35H, dd, J = 5, 14 Hz, $COCHCO_2CH_3$, keto), 3.58 (0.35H, dd, J = 5, 12 Hz, $COCHCO_2CH_3$, keto), 3.02-2.74 (2H, complex), 2.53-2.10 (2H, complex), 2.03-1.66 (2H, complex), 1.26 (1.05H, s, CH_3, keto), 1.24 (0.9H, s, CH_3, enol), 1.11 (1.05H, s, CH_3, keto); hrms M^+: 278.0978 (calcd. for $C_{15}H_{18}O_3S$: 278.0977). Anal. calcd. for $C_{15}H_{18}O_3S$: C 64.73, H 6.52, S 11.50; found: C 64.75, H 6.45, S 11.60.

2-Carbomethoxy-4-methyl-4-[2-(2-thienyl)ethyl]-2,5-cyclohexadienone (72)

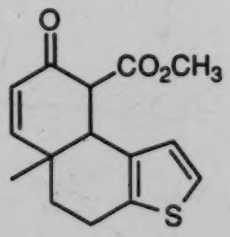


72

Compound **72** was prepared by DDQ oxidation using benzene as a solvent. Treatment of **75** (40 mg, 0.14 mmol) with DDQ (100 mg, 0.42 mmol) for 2 h at

room temperature afforded enone ester **72** (31 mg, 77%): ir (CH_2Cl_2 cast) 2950, 1741 (C=O, ester), 1665 (C=O, enone), 1635 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.50 (1H, d, J = 3 Hz, C**H**=CCO_2CH_3), 7.10 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.88 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.77 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 6.72 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 6.35 (1H, d, J = 10 Hz, CH=C**H**CO), 3.83 (3H, s, OCH_3), 2.74-2.55 (2H, complex), 2.19-2.01 (2H, complex), 1.36 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 181.4 (p), 165.1 (p), 160.0 (a), 152.9 (a), 143.5 (p), 131.8 (p), 130.1 (a), 126.9 (a), 124.5 (a), 123.5 (a), 52.4 (a), 42.2 (p), 42.1 (p), 26.1 (a), 25.9 (p); hrms M^+: 276.0816 (calcd. for $C_{15}H_{16}O_3S$: 276.0820).

9-Carbomethoxy-4,5,5a,8,9,9a-hexahydro-5a-methyl-8-oxo-thieno-[2,3-*h*]naphthalene (76)

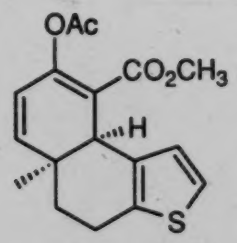


76

Enone ester **72** (38 mg, 0.14 mmol) was treated with stannic chloride (0.032 mL, 0.21 mmol) in dichloromethane (3 mL) at -78°C for 15 min to give tricyclic compound **76** (38 mg, 100%): ir (CH_2Cl_2 cast) 2950, 1743 (C=O, ester), 1678 (C=O, ketone), 1654 (C=O, enol), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of an enol tautomer and two keto epimers in a ratio of 3:3:4,

respectively, δ: 12.08 (0.3H, s, OH), 7.08 (0.7H, d, J = 5 Hz, ArH, keto), 7.00 (0.3H, d, J = 5 Hz, ArH, enol), 6.80 (0.7H, d, J = 10 Hz, CH=CHCO, keto), 6.67 (0.7H, d, J = 5 Hz, ArH, keto), 6.62 (0.3H, d, J = 5 Hz, ArH, enol), 6.11 (0.3H, dd, J = 1, 10 Hz, CH=CHCO, enol), 6.03 (0.7H, d, J = 10 Hz, CH=CHCO, keto), 5.87 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 3.89 (0.9H, s, OCH_3, enol), 3.77 (2.1H, s, OCH_3, keto), 3.62 (0.3H, d, J = 1 Hz, ring junction H, enol), 3.53-3.35 (1.4H, complex, keto), 3.05-2.74 (2H, complex), 2.07-1.70 (2H, complex), 1.17 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 200.6 (p), 194.2 (p), 159.2 (a), 151.6 (a), 148.3 (a), 134.9 (p), 134.7 (p), 127.4 (a), 127.0 (a), 126.0 (a), 125.4 (a), 123.3 (a), 122.1 (a), 59.2 (a), 52.2 (a), 51.6 (a), 43.0 (a), 39.7 (a), 35.8 (p), 35.4 (p), 34.3 (p), 29.5 (p), 25.3 (a), 23.8 (a), 22.9 (p), 22.0 (p); hrms M^+: 276.0819 (calcd. for $C_{15}H_{16}O_3S$: 276.0820).

(5aR*, 9aR*)-8-Acetoxy-9-carbomethoxy-4,5,5a,9a-tetrahydro-5a-methylthieno[2,3-*h*]naphthalene (77)

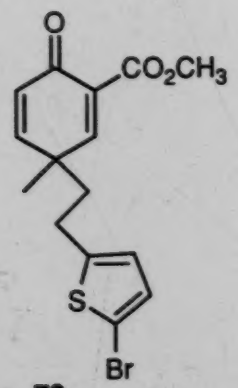


77

Compound **76** (42 mg, 0.15 mmol) was treated with pyridine, a catalytic amount of DMAP and acetic anhydride to give acetate **77** (43 mg, 90%): ir (CH_2Cl_2 cast) 3017 (ArH), 1766 (C=O, $-O_2CCH_3$), 1709 (C=O, CO_2CH_3) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.01 (1H, d, J = 5 Hz, ArH), 6.66 (1H, d, J = 5 Hz, ArH),

6.04 (1H, dd, J = 1.5, 10 Hz, CH=CHCOAc), 5.66 (1H, d, J = 10 Hz, CH=CHCOAc), 3.84 (3H, s, OCH_3), 3.80 (1H, d, J = 1.5 Hz, ring junction H), 2.82 (2H, complex, CH_2), 2.22 (3H, s, O_2CCH_3), 1.95 (2H, complex, CH_2), 1.23 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 168.3 (p), 166.5 (p), 151.9 (p), 145.7 (a), 135.2 (p), 134.7 (p), 126.9 (a), 123.8 (a), 122.2 (a), 114.8 (p), 52.0 (a), 42.2 (a), 36.3 (p), 35.1 (p), 24.4 (a), 22.8 (p), 20.9 (a); hrms M^+: 318.0925 (calcd. for $C_{17}H_{18}O_4S$: 318.0926).

4-{2-[2-(5-Bromothienyl)]ethyl}-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (78)

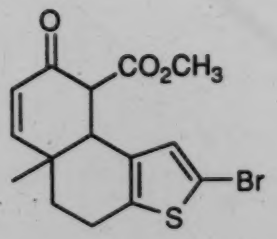


78

To a solution of keto ester **75** (210 mg, 0.75 mmol) in carbon tetrachloride (3 mL) at room temperature under an argon atmosphere and protected from light, was added N-bromosuccinimide (403 mg, 2.26 mmol). The reaction mixture was stirred under the same conditions for 2 h. When the starting material was completely disappeared, the mixture was filtered, the insoluble solid was washed with CCl_4 (5 mL), and the filtrate was concentrated in vacuo. The crude product was then dissolved in dry benzene (3 mL), and DBU (0.34 mL, 2.26

mmol) was added. After being stirred for 4 h at room temperature, water was added to quench the reaction. The aqueous layer was extracted with ethyl acetate (3x5 mL) and the combined organic layers were washed with water, brine and dried over magnesium sulfate. Concentration left a residue which was chromatographed (10% ethyl acetate/hexane) to afford compound **78** (179 mg, 67%): ir (CH_2Cl_2 cast) 1742 (C=O, ester), 1666 (C=O, enone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.47 (1H, d, J = 3 Hz, C**H**=CCO$_2$CH$_3$), 6.81 (1H, d, J = 3.5 Hz, Ar**H**), 6.75 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 6.47 (1H, d, J = 3.5 Hz, Ar**H**), 6.36 (1H, d, J = 10 Hz, CH=C**H**CO), 3.85 (3H, s, OC**H**$_3$), 2.57 (2H, complex, C**H**$_2$), 2.05 (2H, complex, C**H**$_2$), 1.34 (3H, s, C**H**$_3$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 181.3 (p), 164.9 (p), 159.6 (a), 152.7 (a), 145.2 (p), 131.9 (p), 130.2 (a), 129.6 (a), 125.1 (a), 109.5 (p), 52.4 (a), 42.1 (p), 41.8 (p), 26.3 (p), 26.1 (a); hrms M$^+$: 355.9902 (calcd. for $C_{15}H_{15}O_3S^{81}Br$: 355.9904) and 353.9885 (calcd. for $C_{15}H_{15}O_3S^{79}Br$: 353.9925).

2-Bromo-9-carbomethoxy-4,5,5a,8,9,9a-hexahydro-5a-methyl-8-oxo-thieno[2,3-*h*]naphthalene (79)

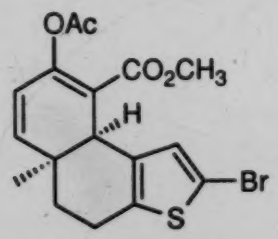


79

Using the general procedure for cyclization, a solution of enone ester **78** (92 mg, 0.26 mmol) in dichloromethane (2 mL) was treated with stannic chloride (0.05 mL, 0.39 mmol) at room temperature for 3 h to provide the tricyclic

compound **79** (92 mg, 100%): ir (CH_2Cl_2 cast) 1743 (C=O, ester), 1655 (C=O, enol ester), 1624 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) the compound existed mostly in the enol form, δ: 12.01 (1H, s, O**H**), 6.54 (1H, s, Ar**H**), 6.09 (1H, dd, J = 1, 10 Hz, C**H**=CHCO), 5.89 (1H, d, J = 10 Hz, CH=C**H**CO), 3.90 (3H, s, OCH_3), 3.56 (1H, d, J = 1 Hz, ring junction **H**), 2.69 (2H, ddd, J = 1.5, 3.5, 8.5 Hz, $ArCH_2$), 2.00-1.78 (2H, complex, CH_2), 1.85 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 173.2 (p), 165.9 (p), 148.1 (a), 137.5 (p), 136.4 (p), 129.8 (a), 123.4 (a), 108.6 (p), 96.1 (p), 51.8 (a), 39.5 (a), 36.4 (p), 35.4 (p), 25.3 (a), 22.8 (p); hrms M^+: 355.9868 (calcd. for $C_{15}H_{15}O_3S^{81}Br$: 355.9904) and 353.9883 (calcd. for $C_{15}H_{15}O_3S^{79}Br$: 353.9925).

(5aR*, 9aR*)-8-Acetoxy-2-bromo-9-carbomethoxy-4,5,5a,9a-tetrahydro-5a-methylthieno[2,3-*h*]naphthalene (80)



80

Following the previously described procedure for acetylation, compound **79** (18 mg, 0.05 mmol) was treated with pyridine and acetic anhydride for 16 h at room temperature to give acetate **80** (18 mg, 90%): ir (CH_2Cl_2 cast) 2952, 1766 (C=O, O_2CCH_3), 1710 (C=O, CO_2CH_3) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 6.61 (1H, s, Ar**H**), 6.03 (1H, dd, J = 1.5, 10 Hz, C**H**=CHCOAc), 5.69 (1H, d, J = 10 Hz,

CH=CHCOAc), 3.84 (3H, s, OCH_3), 3.73 (1H, d, J = 1.5 Hz, ring junction H), 2.72 (2H, ddd, J = 1.5, 3.5, 8.5 Hz, $ArCH_2$), 2.24 (3H, s, CH_3CO_2), 1.95 (2H, complex, CH_2), 1.22 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 168.3 (p), 166.4 (p), 152.1 (p), 145.6 (a), 137.1 (p), 135.4 (p), 129.7 (a), 124.0 (a), 114.4 (p), 108.7 (p), 52.2 (a), 42.0 (a), 36.3 (p), 34.7 (p), 24.3 (a), 22.8 (p), 20.9 (a); hrms M^+: 397.9996 (calcd. for $C_{17}H_{17}O_4S^{81}Br$: 398.0010) and 396.0012 (calcd. for $C_{17}H_{17}O_4S^{79}Br$: 396.0031). Anal. calcd. for $C_{17}H_{17}O_4SBr$: C 51.40, H 4.31, S 8.05; found: C 51.75, H 4.28, S 7.65.

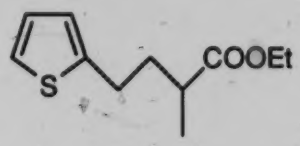
Ethyl 4-(2-thienyl)butanoate (81)

81

In a 100 mL round bottom flask fitted with a total-reflux, variable take-off distillation head was placed a solution of 4-(2-thienyl)butanoic acid (955 mg, 5.61 mmol), *p*-toluenesulfonic acid (107 mg, 0.56 mmol) and 5 mL of ethanol in 20 mL benzene. The mixture was heated to boiling and the azeotrope composed of benzene, alcohol and water was removed at the temperature of approximately 65°C. The mixture was refluxed and stirred for 2 h. Most of the water was removed. The distillation was then stopped, and the residual solution was washed with 10% NaOH saturated with NaCl (4 x 20 mL). The resulting organic solution was then washed with 20 mL portions of water until neutrality and concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an

eluent to afford the ester **81** (1.06 g, 95%): ir (CH_2Cl_2 cast) 2980, 1733 (C=O, ester) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.13 (1H, dd, J = 1, 5.0 Hz, Ar**H**), 6.92 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.80 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 4.13 (2H, q, J = 7 Hz, OCH_2CH_3), 2.88 (2H, t, J = 7.5 Hz, $ArCH_2$), 2.36 (2H, t, J = 7.5 Hz, CH_2CO_2Et), 2.01 (2H, quintet, J = 7.5 Hz, CH_2), 1.26 (3H, t, J = 7 Hz, OCH_2CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 173.3 (p), 144.2 (p), 126.8 (a), 124.5 (a), 123.2 (a), 60.3 (p), 33.4 (p), 29.2 (p), 26.9 (p), 14.3 (a); hrms M^+: 198.0712 (calcd. for $C_{10}H_{14}O_2S$: 198.0715).

Ethyl 2-methyl-4-(2-thienyl)butanoate (82)

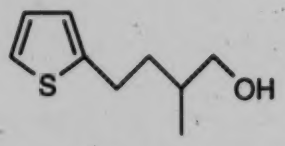


82

To a stirred solution of diisopropylamine (0.17 mL, 1.19 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise a solution of *n*-butyllithium in *n*-hexane (0.38 mL, 0.96 mmol) at 0°C. The resulting mixture was stirred for 15 min at that temperature and then cooled to -78°C with a dry ice-acetone bath. Ethyl 4-(2-thienyl)butanoate **81** (158 mg, 0.80 mmol) in THF (2 mL) was added dropwise, and the mixture stirred for 30 min at -78°C. Methyl iodide (0.07 mL, 1.19 mmol) was added dropwise by a syringe to the above lithium enolate solution with efficient stirring. After being stirred at -78°C for 15 min, the reaction mixture was allowed to gradually warm up to room temperature. Addition of water (5 mL) was followed by stirring for 15 min. The organic phase

was separated and the aqueous layer was extracted with ether (4 x 5 mL), then the combined organic phases were washed with water and brine, and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave a crude oil which was purified by flash chromatography on silica gel eluting with a mixture of ethyl acetate:hexane (5:95) to afford the product **82** (148 mg, 88% yield): ir (CH_2Cl_2 cast) 2977, 1732 (C=O, ester) cm^{-1};^1H nmr ($CDCl_3$, 300 MHz) δ: 7.11 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.91 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.79 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 4.13 (2H, q, J = 7 Hz, $OC\mathbf{H}_2CH_3$), 2.84 (2H, t, J = 8 Hz, $ArC\mathbf{H}_2$), 2.49 (1H, sextet, J = 7 Hz, $C\mathbf{H}CO_2Et$), 2.06 (1H, complex), 1.77 (1H, complex), 1.26 (3H, t, J = 7 Hz, $OCH_2C\mathbf{H}_3$), 1.18 (3H, d, J = 7 Hz, $C\mathbf{H}_3$); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 176.3 (p), 144.4 (p), 126.7 (a), 124.3 (a), 123.1 (a), 60.3 (p), 38.8 (a), 35.6 (p), 27.5 (p), 17.1 (a), 14.3 (a); hrms M^+: 212.0869 (calcd. for $C_{11}H_{16}O_2S$: 212.0871). Anal. calcd. for $C_{11}H_{16}O_2S$: C 62.23, H 7.60, S 15.10; found: C 61.83, 7.83, S 14.63.

2-Methyl-4-(2-thienyl)butanol (83)

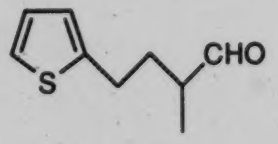


83

A solution of compound **82** (603 mg, 2.84 mmol) in dry diethyl ether (3 mL) was added dropwise to a stirred suspension of lithium aluminum hydride (108 mg, 2.84 mmol) in diethyl ether (10 mL) maintained at 0°C. The resulting mixture was stirred at 0°C for 20 min, then added dropwise ice-cold water (5 mL) at this

temperature. At this point, a white precipitate was formed and later dissolved by adding 10% aqueous HCl solution (5 mL). The organic layer was separated and the aqueous fraction was repeatedly extracted with diethyl ether (4 x 10 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$ and filtered. The solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/hexane (10:90) to give the alcohol **83** (483 mg, 100%): ir (CH_2Cl_2 cast) 3346 (OH) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.11 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.91 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.80 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 3.51 (2H, dq, J = 6, 10.5 Hz, CH_2OH), 2.89 (2H, complex, $ArCH_2$), 1.83 (1H, complex), 1.71 (1H, complex), 1.52 (1H, complex), 1.40 (1H, d, J = 6 Hz, O**H**), 0.98 (3H, d, J = 7 Hz, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 145.5 (p), 126.7 (a), 124.0 (a), 122.9 (a), 68.0 (p), 35.6 (p), 35.2 (a), 27.4 (p), 16.4 (a); hrms M^+: 170.0766 (calcd. for $C_9H_{14}OS$: 170.0765).

2-Methyl-4-(2-thienyl)butanal (84)



84

To a suspension of PCC (1.30 g, 6.0 mmol) in dichloromethane (10 mL) at room temperature was added a solution of alcohol **83** (340 mg, 2 mmol) in dichloromethane (3 mL). After being stirred for 1 hour at room temperture, five-fold of diethyl ether (50 mL) was added, and the resulting mixture was stirred for

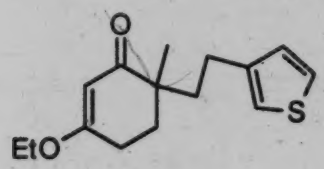
10 min, then filtered through florisil. The solution was concentrated and the crude product was purified by flash chromatography on silica gel, eluting with a mixture of ethyl acetate/hexane (3:97) to afford aldehyde **84** (257 mg, 76%): ir (CH_2Cl_2 cast) 3107 (ArH), 2814, 2713, 1723 (C=O, aldehyde) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 9.63 (1H, d, J = 2 Hz, CHO), 7.14 (1H, dd, J = 1, 5 Hz, ArH), 6.92 (1H, dd, J = 3.5, 5 Hz, ArH), 6.81 (1H, dd, J = 1, 3.5 Hz, ArH), 2.90 (2H, complex, $ArCH_2$), 2.42 (1H, dq, J = 2, 7 Hz, CHCHO), 2.14 (1H, dddd, J = 7, 7, 9, 14 Hz, CH_2), 1.73 (1H, dddd, J = 7, 7, 9, 14 Hz, CH_2), 1.17 (3H, d, J = 7 Hz, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 204.4 (a), 144.0 (p), 126.8 (a), 124.5 (a), 123.3 (a), 45.4 (a), 32.3 (p), 27.2 (p), 13.2 (a); hrms M^+: 168.0607 (calcd. for $C_9H_{12}OS$: 168.0609).

4-Methyl-4-[2-(2-thienyl)ethyl)]-2-cyclohexenone (74) from Aldehyde 84

To a solution of aldehyde **84** (1.10g, 6.55 mmol) in dry benzene (20 mL) was added pyrrolidine (30 mL). The mixture was refluxed overnight with azeotropic removal of water using a Dean-stark apparatus. Most of the solvent was removed by distillation, and the residual solution was concentrated under vacuum at room temperature for 30 min (unable to follow the reaction because the product was hydrolyzed on tlc). The crude mixture was redissolved in benzene cooled to 5°C. Methyl vinyl ketone (6 mL, 39.3 mmol) was added slowly, and the resulting mixture was warmed up to room temperature. After being stirred for 3 h at room temperature, the reaction mixture was quenched with water and separated. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic phases was washed with water, brine and then

dried over $MgSO_4$. The solution was concentrated under reduced pressure. To the solution of this crude mixture in diethyl ether (50 mL) was added silica gel, and the mixture was stirred at room temperature for 45 min. The suspension was filtered, concentrated and the crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give the cyclohexenone **74** (0.923 g, 64% over 3 steps).

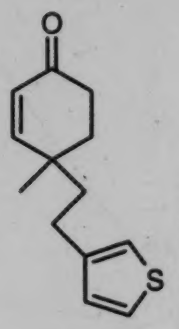
3-Ethoxy-6-methyl-6-[2-(3-thienyl)ethyl]-2-cyclohexenone (86)



86

Alkylation of enone **41** (1.15 g, 7.47 mmol) with LDA (14.94 mmol) and 2-(3-thienyl)ethyl bromide (2.85 g, 11.21 mmol) under reflux for 20 h gave compound **86** (1.24 g, 71% yield based on consumed starting material) along with an 11% recovery of the starting material. Compound **86**: ir (CH_2Cl_2 cast) 2978, 1649 (C=O, enone), 1608 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.23 (1H, dd, J = 3, 5 Hz, Ar**H**), 6.94 (2H, complex, 2 x Ar**H**), 5.27 (1H, s, C=C**H**CO), 3.89 (2H, q, J = 7 Hz, CH_3CH_2O), 2.59 (2H, complex), 2.45 (2H, complex), 2.05-1.73 (4H, complex), 1.36 (3H, t, J = 7 Hz, CH_3CH_2O), 1.14 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 203.7 (p), 175.7 (p), 142.8 (p), 128.3 (a), 125.3 (a), 119.8 (a), 101.4 (a), 64.2 (p), 43.3 (p), 37.8 (p), 32.4 (p), 26.1 (p), 25.0 (p), 22.4 (a), 14.2 (a); hrms M^+: 264.1175 (calcd. for $C_{15}H_{20}O_2S$: 264.1184). Anal. calcd. for $C_{15}H_{20}O_2S$: C 68.15, H 7.63, S 12.13; found: C 67.81, H 7.75, S 12.19.

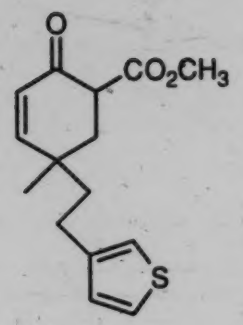
4-Methyl-4-[2-(3-thienyl)ethyl)]-2-cyclohexenone (87)



87

Compound **87** was prepared according to the general procedure for $LiAlH_4$ reduction followed by acid hydrolysis. Compound **86** (1.38 g, 5.30 mmol) was subjected to reduction with $LiAlH_4$ (200 mg, 5.30 mmol), followed by acid hydrolysis to afford enone **87** (960 mg, 84%): ir (CH_2Cl_2 cast) 2956, 1679 (C=O, enone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.26 (1H, dd, J = 3, 5 Hz, Ar**H**), 6.94 (2H, complex, 2 x Ar**H**), 6.71 (1H, d, J = 10 Hz, C**H**=CHCO), 5.91 (1H, d, J = 10 Hz, CH=C**H**CO), 2.68 (2H, complex), 2.49 (2H, complex), 2.05 (1H, ddd, J = 6, 8.5, 14 Hz, CH_2), 1.82 (3H, complex), 1.23 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.4 (p), 158.6 (a), 142.1 (p), 128.0 (a), 127.6 (a), 125.6 (a), 120.0 (a), 41.7 (p), 35.7 (p), 34.1 (p), 33.4 (p), 25.1 (p), 24.8 (a); hrms M^+: 220.0909 (calcd. for $C_{13}H_{16}OS$: 220.0922). Anal. calcd. for $C_{13}H_{16}OS$: C 70.88, H 7.33, S 14.53; found: C 70.79, H 7.45, S 14.77.

6-Carbomethoxy-4-methyl-4-[2-(3-thienyl)ethyl]-2-cyclohexenone (88)

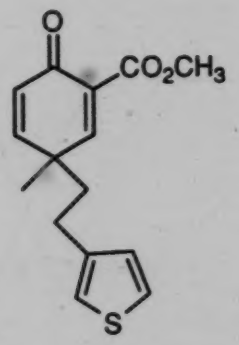


88

The general procedure for carbomethoxylation was used for the preparation of compound **88**. Treatment of **87** (527 mg, 2.39 mmol) with sodium hydride (170 mg, 7.17 mmol) and dimethyl carbonate (20 mL) in THF (50 mL) for 2 h under reflux gave keto ester **88** (472 mg, 71%): ir (CH_2Cl_2 cast) 2952, 1743 (C=O, ester), 1680 (C=O, ketone), 1618 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of three isomers in a ratio of 1:1:1, δ: 11.99 (0.3H, s, OH, enol), 7.27 (1H, complex, ArH), 6.94 (2H, complex 2 x ArH), 6.75 (0.35H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.71 (0.35H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.09 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 5.95 (0.7H, d, J = 10 Hz, CH=CHCO, keto), 5.92 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 3.81 (0.9H, s, OCH_3, enol), 3.78 (2.1H, s, OCH_3, keto), 3.62 (0.35H, dd, J = 5, 14 Hz, $COCHCO_2CH_3$, keto), 3.57 (0.35H, dd, J = 5, 13 Hz, $COCHCO_2CH_3$, keto), 2.07 (2H, complex), 2.40-2.10 (1H, complex), 2.02-1.60 (3H, complex), 1.26 (1.05H, s, CH_3, keto), 1.24 (1.05H, s, CH_3, keto), 1.10 (0.9H, s, CH_3, enol); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 193.8 (p), 193.7 (p), 170.9 (p), 165.1 (p), 158.6 (a), 158.4 (a), 148.0 (a), 142.7 (p), 141.8 (p), 141.7 (p), 128.1 (a), 128.0 (a), 127.9 (a), 126.8 (a), 126.6 (a), 125.8 (a), 125.7 (a), 125.4 (a), 122.0 (a), 120.2 (a), 119.8 (a), 93.0 (p), 65.9 (p), 52.3

(a), 51.4 (a), 50.6 (a), 50.3 (a), 43.4 (p), 41.6 (p), 39.7 (p), 36.8 (p), 36.1 (p), 35.8 (p), 35.5 (p), 32.2 (p), 26.8 (a), 25.7 (a), 25.3 (p), 24.8 (p), 24.0 (a), 15.3 (a); hrms M^+: 278.0969 (calcd. for $C_{15}H_{18}O_3S$: 278.0977). Anal. calcd. for $C_{15}H_{18}O_3S$: C 64.73, H 6.52, S 11.50; found: C 64.47, H 6.50, S 11.16.

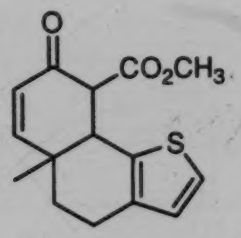
2-Carbomethoxy-4-methyl-4-[2-(3-thienyl)ethyl]-2,5-cyclohexadienone (85)



85

Compound **85** was prepared according to the general procedure for DDQ oxidation using toluene as solvent. Oxidation of keto ester **88** (146 mg, 0.53 mmol) with DDQ (358 mg, 1.59 mmol) for 2 h at -40°C provided dienone ester **85** (114 mg, 78%): ir (CH_2Cl_2 cast) 2949, 1741 (C=O, ester), 1664 (C=O, ketone), 1635 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.50 (1H, d, J = 3 Hz, $CH{=}CCO_2CH_3$), 7.24 (1H, dd, J = 3, 5 Hz, Ar**H**), 6.89 (1H, dd, J = 1, 3 Hz, Ar**H**), 6.86 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.77 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 6.35 (1H, d, J = 10 Hz, CH=C**H**CO), 3.85 (3H, s, OCH_3), 2.45 (2H, complex), 2.03 (2H, complex), 1.36 (3H, s, CH_3); hrms M^+: 276.0795 (calcd. for $C_{15}H_{16}O_3S$: 276.0820).

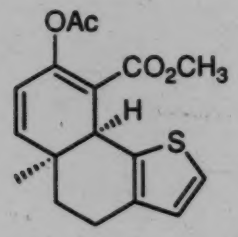
9-Carbomethoxy-4,5,5a,8,9,9a-hexahydro-5a-methyl-8-oxothieno-[3,2-*h*]naphthalene (89)



89

A solution of compound **85** (74 mg, 0.27 mmol) in chloroform (5 mL) was stirred at room temperature for 4 h. After the starting material was completely consumed, the solvent of the reaction mixture was removed under reduced pressure. The crude product was then purified by flash chromatography (ethyl acetate/hexane, 5:95) to give the tricyclic compound **89** (74 mg, 100%): ir (CH_2Cl_2 cast) 2952, 1743 (C=O, ester), 1679 (C=O, ketone), 1657 (C=O, enol), 1627 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) this compound existed mostly in its enol form, δ: 12.06 (1H, br. s, O**H**), 7.07 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.68 (1H, d, J = 5 Hz, Ar**H**), 6.13 (1H, dd, J = 1, 10 Hz, C**H**=CHCO), 5.89 (1H, d, J = 10 Hz, CH=C**H**CO), 3.91 (3H, s, OCH_3), 3.83 (1H, br. d, J = 1 Hz, ring junction **H**), 2.64 (2H, complex), 1.87 (2H, complex), 1.20 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 173.0 (p), 165.8 (p), 148.1 (a), 139.5 (p), 134.6 (p), 126.6 (a), 123.2 (a), 123.0 (a), 97.7 (p), 51.5 (a), 39.8 (a), 37.3 (p), 35.5 (p), 25.8 (a), 23.4 (p); hrms M^+: 276.0824 (calcd. for $C_{15}H_{16}O_3S$: 276.0820). Anal. calcd. for $C_{15}H_{16}O_3S$: C 65.19, H 5.84, S 11.60; found: C 64.95, H 5.86, S 11.23.

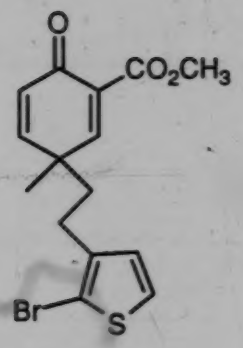
(5aR*, 9aR*)-8-Acetoxy-9-carbomethoxy-4,5,5a,9a-tetrahydro-5a-methylthieno[3,2-*h*]naphthalene (90)



90

Following the general procedure for acetylation reaction, compound **89** (28 mg, 0.10 mmol) was treated with pyridine (3 mL), acetic anhydride (0.1 mL) and a catalytic amount of DMAP to afford acetate **90** (26 mg, 82%): ir (CH_2Cl_2 cast) 2952, 1766 (C=O, CH_3CO_2), 1712 (C=O, CO_2CH_3) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.09 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.69 (1H, d, J = 5 Hz, Ar**H**), 6.07 (1H, dd, J = 1, 10 Hz, C**H**=CHCOAc), 5.69 (1H, d, J = 10 Hz, CH=C**H**COAc), 3.99 (1H, br. d, J = 1 Hz, ring junction **H**), 3.85 (3H, s, OCH_3), 2.66 (2H, complex), 2.23 (3H, s, CH_3CO_2), 1.90 (2H, complex), 1.26 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 168.3 (p), 165.8 (p), 152.4 (p), 145.6 (a), 136.8 (p), 135.2 (p), 126.5 (a), 123.7 (a), 123.4 (a), 115.2 (p), 51.9 (a), 42.2 (a), 37.1 (p), 34.8 (p), 24.9 (a), 23.4 (p), 20.9 (a); hrms M^+: 318.0927 (calcd. for $C_{17}H_{18}O_4S$: 318.0926).

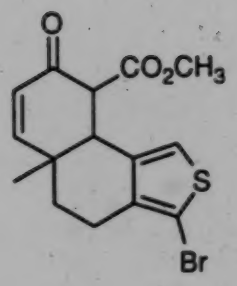
4-{2-[3-(2-Bromothienyl)]ethyl}-2-carbomethoxy-4-methyl-2,5-cyclohexadienone (91)



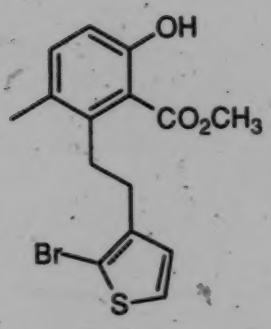
91

According to the procedure described for the preparation of compound **78**, bromination of keto ester **88** (126 mg, 0.45 mmol) with NBS (201 mg, 1.13 mmol) followed by dehydrobromination with DBU (0.14 mL, 0.90 mmol) gave compound **91** (105 mg, 66%): ir (CH_2Cl_2 cast) 3104 (ArH), 1741 (C=O, ester), 1664 (C=O, ketone), 1635 (C=C) cm^{-1}; ^1H nmr (C_6D_6, 300 MHz) δ: 7.05 (1H, d, J = 3 Hz, C**H**=CCO$_2$CH$_3$), 6.61 (1H, d, J = 5.5 Hz, Ar**H**), 6.22 (1H, d, J = 5.5 Hz, Ar**H**), 6.16 (1H, d, J = 10 Hz, CH=C**H**CO), 5.88 (1H, dd, J = 3, 10 Hz, C**H**=CHCO), 3.52 (3H, s, OC**H**$_3$), 2.02 (2H, dd, J = 8.5, 8.5 Hz, ArC**H**$_2$), 1.26 (2H, complex), 0.62 (3H, s, C**H**$_3$); ^{13}C APT nmr (C_6D_6, 75 MHz) δ: 180.6 (p), 165.6 (p), 157.8 (a), 152.1 (a), 140.5 (p), 133.5 (p), 130.0 (a), 128.2 (a), 125.8 (a), 109.7 (p), 51.8 (a), 41.4 (p), 39.9 (p), 25.4 (a), 25.3 (p); hrms M$^+$: 353.9974 (calcd. for $C_{15}H_{15}O_3S^{79}Br$: 353.9925).

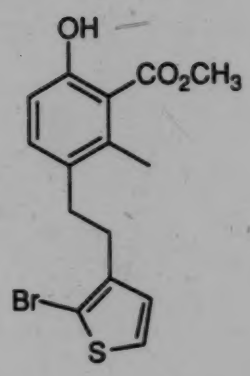
3-Bromo-9-carbomethoxy-4,5,5a,8,9,9a-hexahydro-5a-methyl-8-oxothieno[3,4-*h*]naphthalene (92), methyl 6-hydroxy-2-{2-[3-(2-bromothienyl)]ethyl}-3-methylbenzoate (93) and methyl 6-hydroxy-3-{2-[3-(2-bromothienyl)]ethyl}-2-methylbenzoate (94)



92



93

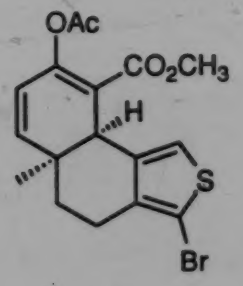


94

Dienone ester **91** (24 mg, 0.07 mmol) was treated with aluminum chloride (18 mg, 0.14 mmol) in ether (5 mL) for 2 h at 0°C to give compound **92** (19 mg, 80%) and an inseparable mixture of **93** and **94** (12:1, 3 mg, 13%). Compound **92**: ir (CH_2Cl_2 cast) 3025, 1742 (C=O, ester), 1680 (C=O, ketone), 1653 (C=O, enol), 1623 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of two keto and enol forms in a ratio of 4:2:4, respectively, δ: 12.04 (0.44H, br. s, O**H**, enol), 6.95 (0.56H, s, Ar**H**, keto), 6.82 (0.56H, d, J = 10 Hz, C**H**=CHCO, keto), 6.78 (0.44H, d, J = 1.5 Hz, Ar**H**, enol), 6.13 (0.44H, dd, J = 1.5, 10 Hz, C**H**=CHCO, enol), 6.03 (0.56H, d, J = 10 Hz, CH=C**H**CO, keto), 5.89 (0.44H, d, J = 10 Hz, CH=C**H**CO, enol), 3.91 (1.32H, s, OCH_3, enol), 3.77 (1.68H, s, OCH_3, keto), 3.56 (1H, br. s, ring junction **H**), 3.52 (0.37H, s, $CHCO_2CH_3$, keto), 3.45 (0.19H, s, $CHCO_2CH_3$, keto), 2.80 (0.56H, ddd, J = 2, 6.5, 18 Hz, $ArCH_2$, keto), 2.72 (0.44H, ddd, J = 2, 5.5, 17 Hz, $ArCH_2$, enol), 2.61-2.32 (1H, complex), 2.02-2.68 (2H, complex), 1.15 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 193.6 (p), 170.6 (p), 165.9 (p), 159.1 (a), 147.7 (a), 141.1 (p), 137.6 (p), 134.6 (p), 126.1 (a), 123.8 (a), 122.8 (a), 121.0 (a), 59.0 (a), 52.2 (a), 51.7 (a), 43.4 (a), 40.5 (a), 36.4 (p), 35.5 (p), 34.9 (p), 29.7 (p), 29.4 (p), 28.6 (p), 25.3 (a), 23.8 (a), 23.3 (p), 22.1 (p); hrms

M^+: 353.9912 (calcd. for $C_{15}H_{15}O_3S^{79}Br$: 353.9925) and 355.9873 (calcd. for $C_{15}H_{15}O_3S^{81}Br$: 355.9905). Compound **93** and **94**: ir (CH_2Cl_2 cast) 2951, 1728 (C=O, ester), 1597 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 10.65 (1H, s, OH), 7.25 (1H, d, J = 8.5 Hz, ArH, phenol ring), 7.23 (1H, d, J = 5.5 Hz, ArH, thiophene ring), 6.83 (1H, d, J = 8.5 Hz, ArH, phenol ring), 6.79 (1H, d, J = 5.5 Hz, ArH, thiophene ring), 4.00 (3H, s, OCH_3), 3.16 (2H, t, J = 8 Hz, CH_2), 2.79 (2H, t, J = 8 Hz, CH_2), 2.34 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 171.1 (p), 160.3 (p), 141.3 (p), 141.1 (p), 136.8 (a), 128.3 (p), 128.1 (a), 125.7 (a), 115.8 (a), 113.0 (p), 109.2 (p), 52.5 (a), 31.7 (p), 29.9 (p), 19.7 (a); hrms M^+: 353.9925 (calcd. for $C_{15}H_{15}O_3S^{79}Br$: 353.9925) and 355.9824 (calcd. for $C_{15}H_{15}O_3S^{81}Br$: 355.9837).

(5aR*, 9aR*)-8-Acetoxy-3-bromo-9-carbomethoxy-4,5,5a,9a-tetrahydro-5a-methylthieno[3,4-*h*]naphthalene (95)

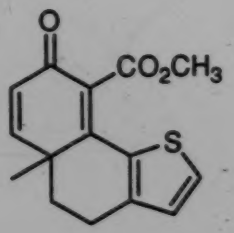


95

By using the general procedure for acetylation, compound **92** (12 mg, 0.03 mmol) was efficiently converted to its corresponding enol acetate **95** (12 mg, 92%): ir (CH_2Cl_2 cast) 2924, 1766 (C=O, CH_3CO_2), 1710 (C=O, CO_2CH_3) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 6.87 (1H, d, J = 1.5 Hz, ArH), 6.07 (1H, dd, J =

1.5, 10 Hz, CH=CHCOAc), 5.69 (1H, d, J = 10 Hz, CH=CHCOAc), 3.84 (3H, s, OCH_3), 3.72 (1H, br. s, ring junction H), 2.73 (1H, ddd, J = 2, 5.5, 18 Hz, $ArCH_2$), 2.44 (1H, ddd, J = 5.5, 13.5, 18 Hz, $ArCH_2$), 2.24 (3H, s, CH_3CO_2), 2.00 (1H, ddd, J = 2, 5.5, 13.5 Hz, CH_2), 1.79 (1H, ddd, J = 5.5, 13.5, 13.5 Hz, CH_2), 1.23 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 168.3 (p), 166.6 (p), 152.1 (p), 145.2 (a), 139.2 (p), 136.6 (p), 124.4 (a), 121.5 (a), 115.5 (p), 107.0 (p), 52.1 (a), 43.0 (a), 36.3 (p), 34.3 (p), 24.4 (a), 23.3 (p), 20.9 (a); hrms M^+: 396.0039 (calcd. for $C_{17}H_{17}O_4S^{79}Br$: 396.0031) and 398.0019 (calcd. for $C_{17}H_{17}O_4S^{81}Br$: 398.0010).

9-Carbomethoxy-4,5,5a,8-tetrahydro-5a-methyl-8-oxothieno[3,2-*h*]naphthalene (96)

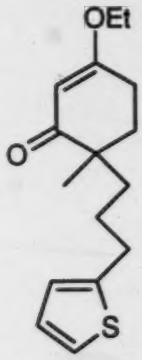


96

Compound **89** (10 mg, 0.04 mmol) was treated with DDQ (24 mg, 0.12 mmol) and acetic acid (1 mL) in THF (4 mL). After 4 days at room temperature, the reaction mixture was filtered, and the solvent was removed under reduced pressure followed by flash chromatography (20% ethyl acetate in hexanes) to give compound **96** (7 mg, 98% yield based on consumed starting material; 3% recovery of the starting material): ir (CH_2Cl_2 cast) 2922, 1732 (C=O, ester), 1651 (C=O, ketone), 1622 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.46 (1H,

d, J = 5 Hz, ArH), 6.92 (1H, d, J = 5 Hz, ArH), 6.86 (1H, d, J = 10 Hz, CH=CHCO), 6.34 (1H, d, J = 10 Hz, CH=CHCO), 3.95 (3H, s, OCH_3), 2.98 (2H, dd, J = 6, 6 Hz, $ArCH_2$), 1.99 (2H, complex, CH_2), 1.32 (3H, s, CH_3); hrms M^+: 274.0663 (calcd. for $C_{15}H_{14}O_3S$: 274.0664).

3-Ethoxy-6-methyl-6-[3-(2-thienyl)propyl]-2-cyclohexenone (98)



98

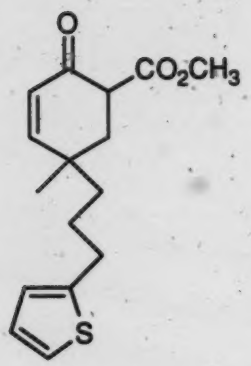
Using the general procedure, alkylation of enone **41** (1.08 g, 7.00 mmol) with LDA (14.0 mmol) and 3-(2-thienyl)propyl bromide (4.62 g, 22.52 mmol) for 16 h in refluxing THF (20 mL) gave compound **98** (1.60 g, 82%): ir (CH_2Cl_2 cast) 2936, 1652 (C=O, enone), 1609 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.09 (1H, dd, J = 1, 5 Hz, ArH), 6.90 (1H, dd, J = 3.5, 5 Hz, ArH), 6.77 (1H, dd, J = 1, 3.5 Hz, ArH), 5.24 (1H, s, C=CHCO), 3.88 (2H, q, J = 7 Hz, CH_3CH_2O), 2.80 (2H, complex), 2.39 (2H, dd, J = 6, 6 Hz, $ArCH_2$), 2.10-1.45 (6H, complex), 1.35 (3H, t, J = 7 Hz, CH_3CH_2O), 1.08 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 204.0 (p), 175.7 (p), 145.3 (p), 126.6 (a), 124.1 (a), 122.8 (a), 101.4 (a), 64.1 (p), 43.2 (p), 36.4 (p), 32.1 (p), 30.4 (p), 26.4 (p), 26.0 (p), 22.4 (a), 14.2 (a); hrms M^+: 278.1342 (calcd. for $C_{16}H_{22}O_2S$: 278.1341).

4-Methyl-4-[3-(2-thienyl)propyl)]-2-cyclohexenone (99)

99

Compound **99** was prepared according to the general procedure for $LiAlH_4$ reduction followed by acid hydrolysis. Compound **98** (810 mg, 2.91 mmol) was subjected to reduction with $LiAlH_4$ (110 mg, 2.91 mmol), followed by acid hydrolysis to afford enone **99** (580 mg, 85%): ir (CH_2Cl_2 cast) 2936, 1681 (C=O, enone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.12 (1H, dd, J = 1, 5 Hz, ArH), 6.92 (1H, dd, J = 3.5, 5 Hz, ArH), 6.79 (1H, dd, J = 1, 3.5 Hz, ArH), 6.66 (1H, d, J = 10 Hz, CH=CHCO), 5.87 (1H, d, J = 10 Hz, CH=CHCO), 2.83 (2H, complex), 2.44 (2H, complex), 1.98 (1H, complex), 1.83-1.47 (5H, complex), 1.14 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 199.5 (p), 158.9 (a), 144.8 (p), 127.4 (a), 126.7 (a), 124.3 (a), 123.1 (a), 40.2 (p), 35.5 (p), 34.1 (p), 33.4 (p), 30.3 (p), 26.4 (p), 24.8 (a); hrms M^+: 234.1082 (calcd. for $C_{14}H_{18}OS$: 234.1078).

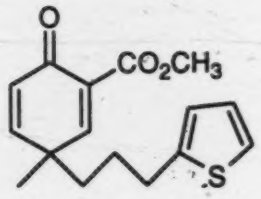
6-Carbomethoxy-4-methyl-4-[3-(2-thienyl)propyl]-2-cyclohexenone (100)



100

The general procedure for carbomethoxylation was used for the preparation of compound **100**. Treatment of **99** (420 mg, 1.80 mmol) with sodium hydride (129 mg, 5.4 mmol) and dimethyl carbonate (10 mL) for 30 min under reflux gave keto ester **100** (484 mg, 92%): ir (CH_2Cl_2 cast) 2936, 1743 (C=O, ester), 1679 (C=O, ketone), 1621 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) a mixture of three isomers in a ratio of 3:4:3, δ: 11.87 (0.3H, s, OH), 7.13 (1H, dd, J = 1, 5 Hz, ArH), 6.93 (1H, dd, J = 3.5, 5 Hz, ArH), 6.79 (1H, br. d, J = 3.5 Hz, ArH), 6.70 (0.3H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.66 (0.4H, dd, J = 2, 10 Hz, CH=CHCO, keto), 6.04 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 5.92 (0.7H, d, J = 10 Hz, CH=CHCO, keto), 5.88 (0.3H, d, J = 10 Hz, CH=CHCO, enol), 3.78 (3H, s, OCH_3), 3.58 (0.4H, dd, J = 4.5, 14 Hz, $COCHCO_2CH_3$, keto), 3.50 (0.3H, dd, J = 5, 13 Hz, $COCHCO_2CH_3$, keto), 2.83 (2H, complex) 2.46-2.17 (1H, complex), 2.13-1.86 (1H, complex), 1.84-1.35 (4H, complex), 1.18 (1.2H, s, CH_3, keto), 1.15 (0.9H, s, CH_3, keto), 1.04 (0.9H, s, CH_3, enol); hrms M^+: 292.1134 (calcd. for $C_{16}H_{20}O_3S$: 292.1133).

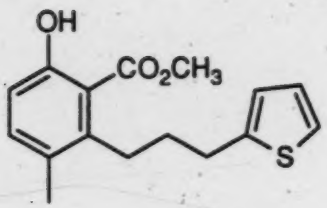
2-Carbomethoxy-4-methyl-4-[3-(2-thienyl)propyl]-2,5-cyclohexadienone (97)



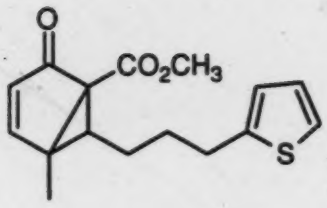
97

Compound **97** was prepared according to the general procedure for DDQ oxidation using benzene as the solvent. Oxidation of keto ester **100** (58 mg, 0.20 mmol) with DDQ (136 mg, 0.60 mmol) in benzene for 2 h gave enone ester **97** (29 mg, 50%): ir (CH_2Cl_2 cast) 2933, 1742 (C=O, ester), 1667 (C=O, ketone) and 1635 (C=C) cm^{-1}; ^1H nmr (C_6D_6, 300 MHz) δ: 6.99 (1H, d, J = 3 Hz, CH=CCO_2CH_3), 6.81 (1H, dd, J = 1, 5 Hz, ArH), 6.72 (1H, dd, J = 3.5, 5 Hz, ArH), 6.35 (1H, dd, J = 1, 3.5 Hz, ArH), 6.12 (1H, d, J = 10 Hz, CH=CHCO), 5.78 (1H, dd, J = 3, 10 Hz, CH=CHCO), 3.85 (3H, s, OCH_3), 2.36 (2H, dt, J = 3, 6 Hz, $ArCH_2$), 1.17-0.97 (4H, complex), 0.55 (3H, s, CH_3); ^{13}C APT nmr (C_6D_6, 75 MHz) δ: 180.7 (p), 165.7 (p), 158.4 (a), 152.8 (a), 144.3 (p), 133.3 (p), 129.7 (a), 127.0 (a), 124.6 (a), 123.4 (a), 51.7 (a), 41.2 (p), 39.3 (p), 29.8 (p), 26.9 (p), 25.3 (a); hrms M^+: 290.0980 (calcd. for $C_{16}H_{18}O_3S$: 290.0977). Anal. calcd. for $C_{16}H_{18}O_3S$: C 66.18, H 6.25, S 11.04; found: C 65.88, H 6.20, S 11.28.

Methyl 6-hydroxy-2-[3-(2-thienyl)propyl]-3-methylbenzoate (101) and 1-Carbomethoxy-5-methyl-6-[3-(2-thienyl)propyl]-bicyclo [3.1.0]hex-3-en-2-one (102)



101



102

A. Using $SnCl_4$ as Lewis acid

A solution of enone **97** (26 mg, 0.09 mmol) in dry dichloromethane (5 mL) was cooled to 0°C under an argon atmosphere. Stannic chloride (0.016 mL, 0.14 mmol) was added, and the mixture was stirred under the same conditions. After 1 h, the starting material was completely consumed. Water was added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic solutions were washed with water, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give compound **101** (9 mg, 35%) and compound **102** (8 mg, 32%). Compound **101**: ir (CH_2Cl_2 cast) 2952, 1732 (C=O, ester), 1596 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 10.59 (1H, s, O**H**), 7.18 (1H, d, J = 10 Hz, Ar**H**, phenol ring), 7.12 (1H, dd, J = 1, 5 Hz, Ar**H**, thiophene ring), 6.92 (1H, dd, J = 3.5, 5 Hz, Ar**H**, thiophene ring), 6.81 (1H, dd, J = 1, 3.5 Hz, Ar**H**, thiophene ring), 6.75 (1H, d, J = 10 Hz, Ar**H**, phenol ring), 3.86 (3H, s, OC**H**3), 2.90 (4H, complex), 2.21 (3H, s, CH_3), 1.86 (2H, complex); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 171.9 (p), 160.2 (p), 145.0 (p), 142.4 (p), 136.7 (a), 128.0 (p), 126.8 (a), 124.4 (a), 123.1

(a), 115.3 (a), 112.9 (p), 52.2 (a), 32.1 (p), 31.4 (p), 30.5 (p), 19.6 (a); hrms M^+: 290.0973 (calcd. for $C_{16}H_{18}O_3S$: 290.0977). Compound **102**: ir (CH_2Cl_2 cast) 2952, 1739 (C=O, ester), 1676 (C=O, enone), 1596 (C=C) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.13 (1H, dd, J = 1, 5 Hz, ArH), 6.90 (1H, dd, J = 3.5, 5 Hz, ArH), 6.81 (1H, multiplet, ArH), 6.66 (1H, dd, J = 2, 10 Hz, CH=CHCO), 6.25 (1H, d, J = 10 Hz, CH=CHCO), 3.69 (3H, s, OCH_3), 2.83 (1H, complex), 2.40 (1H, dd, J = 1, 13 Hz), 2.00 (1H, complex), 1.83 (2H, complex), 1.59 (2H, complex), 1.23 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 194.0 (p), 172.6 (p), 155.4 (a), 143.7 (p), 131.7 (a), 126.2 (a), 125.9 (a), 123.8 (a), 60.4 (p), 52.3 (a), 46.5 (p), 40.9 (a), 35.0 (p), 33.9 (p), 28.1 (p), 28.0 (a); hrms M^+: 290.0972 (calcd. for $C_{16}H_{18}O_3S$: 290.0977).

B. Using $AlCl_3$ as Lewis acid

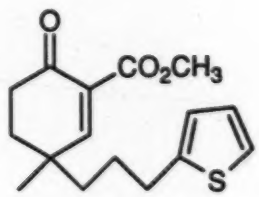
To a stirred suspension of anhydrous aluminun chloride (30 mg, 0.23 mmol) in dry diethyl ether (5 mL) at 0°C under an argon atmosphere, was added a solution of enone ester (44 mg, 0.15 mmol) in diethyl ether (2 mL). The reaction mixture was stirred at 0°C for 1 h and then quenched with ammonium chloride solution, followed by addition of water. The aqueous solution was extracted with diethyl ether (3 x 5 mL). The organic solution was washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to afford compound **101** (28 mg, 64%).

4-Methyl-4-[3-(2-thienyl)propyl)]cyclohexanone (104)

104

Reduction of enone **99** (43 mg, 0.18 mmol) with Wilkinson's catalyst (34 mg, 0.04 mmol) in dry benzene at room temperature and under hydrogen atmosphere (2 atm) for 16 h gave a quantitative yield of ketone **104** after filtration, concentration and chromatographic purification (43 mg, 100%): ir (CH_2Cl_2 cast) 2954, 1716 (C=O, ketone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.02 (1H, dd, J = 1, 5 Hz, ArH), 6.83 (1H, dd, J = 3.5, 5 Hz, ArH), 6.71 (1H, dd, J = 1, 3.5 Hz, ArH), 2.76 (2H, dd, J = 7, 7 Hz, $ArCH_2$), 2.23 (4H, complex), 1.60 (4H, complex), 1.37 (2H, complex), 1.20 (2H, complex), 0.92 (3H, s, CH_3); hrms M^+: 236.1239 (calcd. for $C_{14}H_{20}OS$: 236.1235).

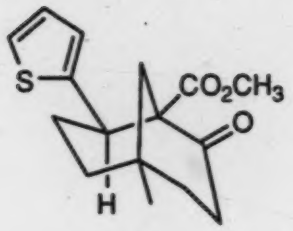
2-Carbomethoxy-4-methyl-4-[3-(2-thienyl)propyl]-2-cyclohexenone (103)



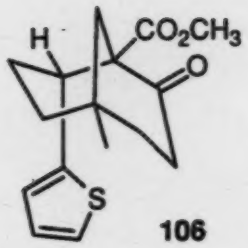
103

Compound **103** was prepared according to the general procedure for carbomethoxylation followed by DDQ oxidation. Ketone **104** (52 mg, 0.22 mmol) was subjected to carbomethoxylation with sodium hydride (16 mg, 0.66 mmol) and dimethyl carbonate (10 mL) under reflux. After 0.5 h, the starting material was completely consumed and the reaction mixture was cooled to 0°C. Water was added to quench the reaction. The resulting aqueous solution was extracted with diethyl ether (3 x 10 mL), and the combined organic extracts were washed with water and brine, dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The crude product was then dissoved in benzene (5 mL). To this solution at room temperature under an argon atmosphere, was added DDQ (145 mg, 0.63 mmol). The mixture was stirred for 0.5 h at room temperature and the precipitate was removed by filtration. The filtrate was concentrated, and the crude product was subjected to flash chromatography using ethyl acetate/hexane (20:80) as an eluent to give the enone ester **103** (33 mg, 51%): ir (CH_2Cl_2 cast) 1743 (C=O, ester), 1686 (C=O, ketone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.35 (1H, s, C**H**=CCO_2CH_3), 7.13 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.92 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.79 (1H, br. d, J = 3.5 Hz, Ar**H**), 3.79 (3H, s, OCH_3), 2.86 (2H, dd, J = 7, 7 Hz, $ArCH_2$), 2.51 (2H, complex), 1.99 (1H, ddd, J = 6, 9, 14 Hz, CH_2), 1.85-1.51 (5H, complex), 1.19 (3H, s, CH_3); hrms M^+: 292.1131 (calcd. for $C_{16}H_{20}O_3S$: 292.1133).

(1S*, 5S*, 8R*)-1-Carbomethoxy-5-methyl-8-(2-thienyl)bicyclo-[3.3.1]nonan-2-one (105) and (1S*, 5S*, 8S*)-1-carbomethoxy-5-methyl-8-(2-thienyl)bicyclo[3.3.1]nonan-2-one (106)



105



106

To a solution of enone ester **103** (20 mg, 0.07 mmol) in dichloromethane (5 mL) at -78°C was added stannic chloride (0.012 mL, 0.1 mmol). The reaction mixture was allowed to warm up to room temperature and stirred for 1 h. After cooling to 0°C, water was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic solutions were washed with water, dried over magnesium sulfate and filtered. The crude product was purified by flash chromatography using ethyl acetate/hexane (10:90) as an eluent to give compound **105** (11 mg, 55%) and its diastereomer **106** (5 mg, 25%). Compound **105**: ir (CH_2Cl_2 cast) 3070 (ArH), 1738 (C=O, ester), 1710 (C=O, ketone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.11 (1H, dd, J = 1, 5 Hz, Ar**H**), 6.88 (1H, dd, J = 3.5, 5 Hz, Ar**H**), 6.81 (1H, dd, J = 1, 3.5 Hz, Ar**H**), 3.61 (3H, s, OCH_3), 3.60 (1H, dd, J = 5, 13 Hz, Ar**CH**), 2.67-2.38 (2H, complex), 2.23 (1H, dd, J = 2.5, 13.5 Hz, C9-**H**), 2.10-1.68 (6H, complex), 1.55 (1H, dd, J = 5.5, 13.5 Hz, C9-**H**), 1.02 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 207.2 (p), 172.5 (p), 144.5 (p), 126.2 (a), 125.5 (a), 123.7 (a), 62.3 (p), 52.2 (a), 45.3 (p), 42.7 (a), 39.9 (p), 39.4 (p), 34.1 (p), 31.7 (a), 29.9 (p), 29.4 (p); hrms M^+: 292.1137 (calcd. for $C_{16}H_{20}O_3S$: 292.1133). Compound **106**: ir (CH_2Cl_2 cast) 2949, 1750 (C=O, ester), 1714 (C=O, ketone) cm^{-1}; ^1H nmr ($CDCl_3$, 300 MHz) δ: 7.15 (1H, dd, J = 3.5, 3.5 Hz, Ar**H**), 6.95 (2H,

d, J = 3.5 Hz, 2 x ArH), 4.04 (1H, br. d, J = 4.5 Hz, ArCH), 3.52 (3H, s, OCH_3), 2.69 (1H, ddd, J = 10, 10, 16 Hz, C3-H), 2.42 (1H, ddd, J = 4, 7, 16 Hz, C3-H), 2.32 (1H, ddd, J = 2, 2, 14.5 Hz, C9-H), 2.07 (1H, dd, J = 1, 14.5 Hz, C9-H), 1.94-1.58 (5H, complex), 1.36 (1H, complex), 1.10 (3H, s, CH_3); ^{13}C APT nmr ($CDCl_3$, 75 MHz) δ: 209.6 (p), 169.8 (p), 144.0 (p), 126.6 (a), 126.2 (a), 123.8 (a), 61.6 (p), 52.3 (a), 41.6 (a), 38.4 (p), 36.1 (p), 35.6 (p), 33.0 (p), 32.6 (a), 29.4 (p), 27.6 (p); hrms M^+: 292.1129 (calcd. for $C_{16}H_{20}O_3S$: 292.1133).

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